Chapter 8

Cardiovascular Health Effects

8.0 Introduction

In this chapter, epidemiologic studies and other human data regarding the relationship between coronary heart disease (CHD) and exposure to environmental tobacco smoke (ETS) by nonsmokers are reviewed and the overall weight of evidence for an association is presented. In addition to the human evidence, there is confirmatory animal evidence (e.g., Glantz and Parmley, 1991 and 1995), which is summarized briefly.

CHD includes a spectrum of clinical manifestations, the major forms of which are myocardial infarction (MI), angina pectoris (AP), and sudden unexpected death (SUD) which occurs in persons with no prior history of CHD. Etiology for the various heart disease endpoints and their occurrence have been examined in detail (U.S. DHHS, 1983; U.S. DHHS, 1990; Kannel, 1976). Different terms have been used to represent CHD in the literature, including ischemic heart disease (IHD), and arteriosclerotic heart disease (AHD). For uniformity, CHD will be used throughout this chapter. Results by specific endpoints (i.e., MI, SUD, or AP) or for cardiovascular mortality versus morbidity will be presented separately when such data are available.

8.0.1 Active Smoking

A causal association between active smoking and CHD is well established (U.S. DHHS, 1983; U.S. DHHS, 1990). Evidence from case-control and cohort studies has clearly revealed a higher risk of MI, SUD, and other deaths from CHD in cigarette smokers than in nonsmokers. Although smoking clearly provokes AP (Friedman *et al.*, 1975), and risks of AP are elevated in smokers compared to nonsmokers in some studies (Willett *et al.*, 1987; Beard *et al.*, 1989; Hagman *et al.*, 1987), this association has not been observed consistently and the association with smoking tends to be weaker for AP than for other heart disease endpoints (Kannel, 1976; 1981). The excess risk of CHD morbidity and mortality in relation to smoking extends to all age groups, to both genders and to populations within and outside the U.S. The data are generally supportive of a dose-response relationship in that the risks increase with increasing duration of smoking, increasing number of cigarettes smoked, and with depth of inhalation.

8.0.2 Previous Reviews on Environmental Tobacco Smoke and Coronary Heart Disease in Nonsmokers

Since 1984 some 18 studies have examined the association between environmental tobacco smoke (ETS) and risk of CHD in nonsmokers. In 1986, this literature was first reviewed qualitatively in A Report of the Surgeon General (U.S. DHHS, 1986) and a report of the National Research Council (NRC, 1986). Available for the 1986 reviews were data from three cohort studies (Hirayama, 1984; Gillis *et al.*, 1984; Garland *et al.*, 1985) and one case-control study (Lee *et al.*, 1986). The conclusion of both 1986 reviews was that an association between ETS and CHD was biologically plausible but the epidemiological evidence was inconclusive. A 1990

review (Wu-Williams and Samet, 1990) included results from two additional cohort studies (Svendsen *et al.*, 1987; Helsing *et al.*, 1988). These authors concluded that in all "prospective studies, there was an excess of heart disease mortality among nonsmokers with ETS exposure although the exposure-response relationship is not clear."

In addition, five more quantitative reviews have been published: Wells (1988); Glantz and Parmley (1991); Steenland (1992); Wells (1994); Glantz and Parmley (1995). Four of these reviews included a meta-analysis to calculate a pooled relative risk for CHD in relation to ETS exposure (Wells, 1988; Glantz and Parmley, 1991; Wells, 1994; Glantz and Parmley, 1995). The 1988 review by Wells included 5 cohort studies (Hirayama, 1984; Gillis *et al.*, 1984; Garland *et al.*, 1985; Svendsen *et al.*, 1987; Helsing *et al.*, 1988) and two case-control studies (Lee *et al.*, 1986; Martin *et al.*, 1986 (unpublished)). Based on 1522 CHD events in females and 443 CHD events in males, Wells (1988) calculated that the odds ratio (OR) for CHD in relation to ETS exposure was 1.23 (95% CI=1.1, 1.4) for females and 1.31 (95% CI=1.1-1.6) for males.

The subsequent review by Glantz and Parmley (1991a) summarized results from ten studies; four were new studies published between 1989 and 1990 which were not covered in previous reviews (He *et al.*, 1989; Hole *et al.*, 1989; Humble *et al.*, 1990; Butler, 1988). These authors presented results from the individual studies, separately for males and females, and calculated a significantly elevated pooled risk estimate for males (relative risk (RR) = 1.3, 95% CI= 1.1-1.6), for females (RR=1.3, 95% CI=1.2-1.4), and both genders combined (RR=1.3, 95% CI=1.2-1.4). This review also discussed possible mechanisms for an ETS effect on heart disease in nonsmokers. An updated review of this subject was published by the same authors in 1995 (Glantz and Parmley, 1995).

Wells' 1994 review included results from 13 studies; eight of these studies were not included in his 1988 review (Hole *et al.*, 1989; Humble *et al.*, 1990; Butler, 1988; Dobson *et al.*, 1991a; He *et al.*, 1994; La Vecchia *et al.*, 1993; Jackson, 1989; Sandler *et al.*, 1989 (this covered the same study as Helsing *et al*., 1988). Pooled risk estimates for CHD morbidity and mortality in relation to ETS exposure for males and females separately and combined were presented. Risk estimates were presented with and without correction for misclassification bias of smokers as nonsmokers. In women the OR was 1.51 (95% CI=1.2-2.0) for CHD morbidity and 1.23 (95% CI=1.11-1.36) for CHD mortality in association with ETS exposure. The corresponding ORs in men were 1.28 (95% CI=0.91-1.81) and 1.25 (95% CI=1.03-1.51). The ORs for CHD morbidity and mortality in women and men were almost unchanged after correction for misclassification bias.

Also included in some of these reviews were estimates of the number of CHD deaths in nonsmokers that could be attributed to ETS exposure (Wells, 1988; Steenland, 1992; Wells, 1994). Steenland's review (1992)[a] covered essentially the same studies as the review by Glantz and Parmley (1991a), and in addition, estimated the number of CHD deaths in nonsmokers and former smokers that could be attributable to ETS. Steenland concluded that some 28,000 deaths in U.S. never-smokers and 19,500 deaths in U.S. former smokers (who had stopped smoking at

[a] Steenland's review included a 1991 study (Dobson *et al.*, 1991), excluded the abstract by Butler (1988), and did not cite Gillis *et al.* (1984) who presented preliminary findings on the same study population covered by Hole *et al.* (1989).

least 15 years before the study) could be attributed to exposure to ETS. To conduct this analysis, Steenland applied the age- and sex-specific CHD rates for U.S. never-smokers estimated from cohort studies conducted in the 1970s and 1980s, the prevalence of exposure to ETS among nonsmoker controls reported in case-control studies conducted during the same time period, and the relative risk of CHD in nonsmokers associated with ETS exposure from the study by Helsing *et al.* (1988), the largest U.S. study on ETS and risk of CHD in nonsmokers. These results are very similar to those presented by Wells (1988; 1989; 1990) who used somewhat different methods and assumptions in his calculations. Wells (1994) estimated that 62,000 deaths from ischemic heart disease in the U.S. in 1985 were due to ETS exposure. One possible reason for the considerably higher estimate in the 1994 review is the higher CHD death rates overall and in never smokers in 1985 compared to the never-smoker death rates that were used in the earlier risk assessments. Moreover, Wells (1994) assumed that the ETS exposure from background sources (i.e., other than from spouses) was higher than that assumed in the previous reviews and applied methodology that U.S. EPA (1992) used in estimating the lung cancer burden of ETS exposure.

The conclusions of the reviews by Glantz and Parmley (1991a) and Steenland (1992) were endorsed by the American Heart Association (Taylor *et al.*, 1992). However, critics of the review by Glantz and Parmley (Huber and Brockie, 1991; Simmons, 1991; Holcomb, 1991; Decker, 1991; Mantel, 1992) questioned the reviewers' interpretation of the epidemiological data and the meaningfulness of relative risk estimates that were less than three. They also questioned the authors' method of deriving the pooled risk estimate, and the inclusion of 'positive' findings that were not statistically significant. The critics attributed the observed association between ETS and heart disease to biases, including inadequate adjustment or lack of adjustment for potential confounders in some studies. Glantz and Parmley (1991b, 1991c, 1992) discounted these criticisms in their responses. A second line of criticism questioned the fundamental relationship between active smoking and CHD in women (Seltzer, 1991a and 1991b) and whether the magnitude of effect observed between CHD and passive smoking is plausible after asserting that the association with active smoking is relatively weak (Mantel, 1992; Skrabanek, 1992).

8.0.3 Chapter Overview

This chapter will include, first, a description of each of the studies on ETS and CHD in terms of the design of study, measures of exposures, information on potential confounders, and the main study findings (Section 8.1). The studies included in this review represent all the published studies on this topic that had been included in either the review by Glantz and Parmley (1991) or by Steenland (1992), as well as five case control studies (Jackson *et al.*, 1991; He *et al.*, 1994; La Vecchia *et al.*, 1993; Layard, 1995; Muscat and Wynder, 1995), two analyses of the same cohort data set (LeVois and Layard, 1995; Steenland *et al.*, 1996), and a recent report of a cohort analysis (Kawachi *et al.*, 1997) of the Nurses' Health Study. Second, in Section 8.2 the effect of bias on the risk estimates in these studies will be discussed. The main sources of bias of concern are misclassification of smokers as nonsmokers, the lack of control for potential confounders, and misclassification of ETS exposure. Also in Section 8.2, the biological plausibility of an association between ETS and CHD will be discussed by comparing this to the association between active smoking and CHD. Finally, in Section 8.3 supportive data, primarily the acute

effects of ETS on cardiovascular function in nonsmokers will be presented. These include a discussion of the effects of ETS exposure on internal and common carotid wall thickness, endothelium function, exercise tolerance, lipid profile, platelet function and fibrogen levels.

8.1 Description of Epidemiologic Studies

The relationship between CHD in nonsmokers and ETS has been examined in ten cohort and eight case-control studies. Eight of the cohort studies were conducted in the United States, one in Japan, and one in Scotland. The case-control studies were conducted in the United Kingdom, China, Australia, New Zealand, Italy and the United States.

8.1.1 Cohort studies

Japanese cohort study *(Hirayama, 1981; 1984; 1990)*

In the Japanese cohort study (Hirayama, 1984), adults at least 40 years of age and residents in one of 29 health center districts in Japan were enrolled in 1965. About 90% of the targeted population participated in the study and completed a questionnaire on various lifestyle factors, including smoking and drinking habits, and occupational history. Mortality of the cohort was monitored by review of the annual census of residents and death certificates. The relationship between CHD mortality and ETS was evaluated in cohort subjects followed between 1966 and 1981.

There were 494 deaths from CHD identified among 91,540 lifetime non-smoking women. Compared to nonsmoking women married to nonsmokers, women married to exsmokers or smokers of 1-19 cigarettes/day, and smokers of 20+ cigarettes/day, showed relative risks of 1.10 (90% CI=0.91, 1.33), and 1.31 (90% CI=1.06, 1.63), respectively, for CHD (1-sided p for trend = 0.019) (Hirayama, 1984). The increase in relative risk of CHD in relation to husband's smoking was observed when the analysis was adjusted for husband's age (40-49, 50-59, 60-69, 70+) and occupation (Table 8.1). A later update (Hirayama, 1990) showed that similar results were observed when adjustment was made for wives' age. Despite the strengths of a large sample size of nonsmoking women and of CHD deaths in this cohort, the study’s value is lessened by the lack of information on potential confounders of CHD which made it impossible to adjust for other heart disease risk factors in the analysis.

Lee (1990) questioned the results of this study because the analysis based on 14 years of follow-up data (i.e., from 1966-1979) did not yield a statistically significant association whereas the results based on 16 years of follow-up data (i.e., with an additional 94 CHD deaths between 1980-1981) were statistically significant. This criticism is ill-founded since the results based on 14 years of follow-up (and 410 CHD deaths) showed the same pattern of increased risks: the RRs were 1.05 (90% CI=0.86-1.29), and 1.21 (90% CI=0.95-1.53) when husbands were exsmokers or smoked 1-19 cigarettes/day, and 20+ cigarettes/day, respectively, compared to husbands who did not smoke (Hirayama, 1990). However, what is unclear and warrants explanation is the discrepancy in the results based on 14 years of follow-up in Hirayama's first report (1981) and his second report (Hirayama, 1984). In the 1981 report, Hirayama found RRs of 0.97 when husbands were exsmokers or smoked 1-19 cigarettes/day and 1.03 for 20+ cigarettes/day (p value = 0.39) (based on 406 CHD deaths).

San Diego study *(Garland et al., 1985)*

A second report on the role of ETS and heart disease utilized data collected in a cohort of predominantly white, upper middle-class subjects in San Diego (Garland *et al.*, 1985). This cohort was established between 1972 and 1974 and successfully enrolled 82 percent of the subjects contacted. A standardized interview was administered and covered cigarette use, past hospitalizations for heart attack, heart failure, or stroke, and duration of marriage. Questions on smoking included smoking status at enrollment (current, former, or never) and among current smokers, the number of cigarettes smoked per day. In addition, blood pressure, weight, height, and plasma cholesterol were measured at study enrollment.

The analysis on ETS and heart disease was based on 695 married nonsmoking women, classified by their husband's self-reported smoking status at enrollment and excluded women who had a history of heart disease or stroke, or had smoked. Vital status of the cohort was determined by annual mailings for 10 years. Follow-up was almost complete and death certificates were obtained for all deaths. After 10 years of follow-up, there were 19 deaths due to CHD (International Classification of Diseases, Adapted (ICDA) 410.0-414.9) among nonsmoking married women. The age-adjusted mortality rates were 1.2, 3.6 and 2.7, respectively, for women married to nonsmokers, exsmokers, and current smokers (one-sided p for trend, ≤ 0.10). The corresponding RRs for the adjusted mortality rates were 1.0, 3.0, and 2.3. The relative risk for CHD mortality among women married to current or former smokers compared to women married to never smokers was 2.7 (p value ≤ 0.10) after adjustment for age, systolic blood pressure, total plasma cholesterol, obesity index, and years of marriage (Table 8.1).

Most of the information on CHD risk in this study was based on nonsmoking women married to exsmokers at study enrollment. A possible explanation for the higher risk among nonsmoking women married to former smokers than to current smokers is that this group of husbands had been very heavy smokers and had stopped smoking for health reasons. Thus, wives of these former smokers may had been heavily exposed. The findings in relation to any ETS exposure are only suggestive given the small numbers of CHD deaths and that the analysis was conducted by husbands' smoking status, and not amount smoked by husbands.

MRFIT - 18 cities study *(Svendsen et al., 1987)*

The role of ETS and risk of heart disease was evaluated in a cohort of men aged 35-57 years who were recruited in 18 U.S. cities beginning in 1973 for the Multiple Risk Factor Intervention Trial (MRFIT) (Svendsen *et al.*, 1987). At enrollment, extensive information was collected, including smoking history of the index subjects, and of their wives, family members, and coworkers. In addition, markers of exposure to tobacco smoke, including serum thiocyanate and expired air carbon monoxide were measured, and pulmonary function tests were conducted. Pulmonary function tests and measurements of thiocyanate were conducted at entry into the study (baseline) and at each of six annual examinations, whereas expired carbon monoxide was measured at baseline, and at the third and sixth examination.

Cause of death was classified by a committee of three cardiologists who reviewed the hospital/physician records, death certificates, autopsy reports, and next-of-kin interviews. Subjects were followed an average of 7 years and the effect of ETS was investigated for CHD

death (including documented MI, SUD, congestive heart failure, and death associated with surgery for CHD), and fatal or nonfatal CHD events combined.

Analyses were conducted for never smokers and all nonsmokers at entry (i.e., exsmokers who stopped prior to entry into the study). Of the 12,866 men, there were 1,245 married men who never smoked of whom 286 were married to smokers and 959 to nonsmokers. Among men who never smoked, there were 13 deaths due to CHD and 56 nonfatal CHD events (Table 8.1). Compared to men married to nonsmokers, men married to smokers showed a higher risk of death from CHD (adjusted RR=2.23, 95% CI=0.72-6.92) and for fatal and nonfatal CHD combined (adjusted RR=1.61, 95% CI=0.96-2.71) after adjusting for other risk factors for heart disease (age, blood pressure, cholesterol, weight, drinks per week, and education). The adjusted relative risks were slightly higher than the unadjusted values.

The effect of ETS exposure from wives' smoking was also evaluated among all nonsmoking men. Both men who never smoked and those who stopped smoking prior to entry into the study were included (numbers of subjects and number of CHD events in the latter group were not specified). Non-smoking men whose wives smoked showed a higher risk of death from CHD (adjusted RR=1.59, 95% CI=0.84-3.02) and a higher risk of fatal and nonfatal CHD combined (adjusted RR=1.32, 95% CI=0.95-1.84) compared to men whose wives did not smoke. However, these risk estimates are lower than those presented above for men who never smoked, suggesting that the effect due to ETS exposure may have been diluted substantially by including exsmokers in the analysis.

In the same study, there is a suggestion of an ETS effect from coworkers' smoking after adjusting for age and wives' smoking habits (these RRs were presumably not adjusted for other CHD risk factors). The adjusted RR was 2.6 (95% CI=0.5-12.7) for CHD death and 1.4 (95% CI=0.8-2.5) for fatal or nonfatal CHD combined for men who never smoked but were exposed to coworkers' smoking. The joint effect of ETS exposure from wives and coworkers was also evaluated. Relative to men whose wives and coworkers did not smoke, the RRs for fatal and nonfatal CHD combined were 1.0 (95% CI=0.5-1.9) when coworkers smoked but wives did not, 1.2 (95% CI=0.4-3.7) when wives smoked and coworkers did not, and 1.7 (95% CI=0.8-3.6) when both smoked.

This study has several strengths. First, misclassification of active smokers as nonsmokers is minimized since there were baseline and regular measurements of various biomarkers to assess long-term (based on thiocyanate) and short-term (based on carbon monoxide) exposure to tobacco smoke. In this study, nonsmoking men married to smokers had significantly higher levels of expired air carbon monoxide, significantly lower levels of maximum FEV_1, and thiocyanate levels comparable to those of nonsmoking men married to nonsmokers. Although thiocyanate is not specific to ETS exposure and is not considered a sensitive marker for exposure to ETS, serum thiocyanate levels have been used successfully to distinguish between active smokers and nonsmokers (U.S. DHHS, 1986). Second, ETS exposure was based on both wives' and coworkers' smoking habits at baseline, thus covering the main sources of domestic and non-domestic exposure. Third, information on potential confounders for CHD was available. At entry into the study, nonsmoking men married to smokers were similar to those married to nonsmokers in age, diastolic or systolic blood pressure, total, high and low density lipoprotein

cholesterol, and income, but differed significantly in weight (heavier), drinking habits (drank more), and education (fewer years). However, the differences in weight and drinking habits between the two groups did not persist by the sixth annual examination. The effect of ETS was observed when potential confounders for heart disease, education, and measures of social class were accounted for in the analysis. Finally, this study examined the effect of ETS on both fatal and non-fatal CHD events. Point estimate of risks were higher for fatal events than for fatal and nonfatal events combined, suggesting that the association between ETS exposure and nonfatal events may be relatively weak (adjusted RRs were not presented separately for nonfatal events).

The main limitation of this study is that this study population may be unrepresentative of the general population. Men selected in the MRFIT study were already at high-risk of heart disease, defined by their levels of serum cholesterol and diastolic blood pressure.

Maryland study *(Helsing et al., 1988)*

The role of ETS in the etiology of heart disease mortality in men and women was investigated by Helsing *et al.* (1988), who utilized data from a private census conducted in 1963 covering some 98 percent of the households in Washington County, Maryland. The subcohort for this analysis comprised of 3,454 males and 12,345 females who never smoked, and were available for follow-up in 1971. These subjects were followed between 1963-1975 and the risk of heart disease mortality was evaluated relative to their household exposure to ETS. CHD listed as an underlying or contributing cause of death was included as a heart disease mortality outcome.

Information on sex, age, race, marital status, years of schooling, and housing characteristics were available and were adjusted for in the analyses. Use of any tobacco products, including cigarettes, cigars, and pipes was recorded for all subjects and their household members. In brief, a score ranging from 0 to 12 was assigned to each adult in the household based on his/her smoking history. A total household smoking score was then calculated by summing the smoking contribution scores of all persons living in that household. Each individual's household ETS exposure was calculated by subtracting his or her own contribution to the total household score. Among nonsmoking men, 29.5% reported any household exposure to ETS compared to 65.5% among nonsmoking women.

In the never smokers there were a total of 370 deaths in men and 988 in women for whom CHD was listed as the underlying cause of death. The adjusted relative risk for any ETS exposure was 1.31 (95% CI=1.1-1.6) for men and 1.24 (95% CI=1.1-1.4) for women. (Note: in Sandler *et al.* (1989), the RR in women was 1.19 (95% CI = 1.04-1.35); the reason for the discrepancy is not known.) There was no clear dose-response trend with increasing ETS exposure in men (i.e., scores of 0, 1-5, 6+), but there was some suggestion of a trend in women (Table 8.1). When data were stratified by gender and by age of study subjects at enrollment in 1963 (25-44, 45-54, 55-64, and 65+), risk for CHD in relation to ETS exposure was increased in 7 of 8 age-sex groups. The RRs were increased in all age groups of men exposed to ETS and were statistically significant for two subgroups. In women, increased risks were observed in all but the 55-64 age group and the results were statistically significant for the 65+ age group. Results were similar when the analyses included all deaths with CHD listed as the underlying or contributing cause of death (i.e., a total of 461 and 1,281 deaths in nonsmoking men and women, respectively).

This is one of the larger studies on ETS and heart disease in nonsmoking men and women. The larger sample size allowed analysis stratified by age group and by sex. In addition, exposure to ETS included all household exposures. Unfortunately, the effect due to spouse's smoking alone, typically used as a measure of ETS exposure in other studies, was unavailable for comparison. Data on potential confounding factors for heart disease were not collected so that the RRs were adjusted for demographic factors only.

Scottish study *(Hole et al., 1989)*

This study was conducted to investigate the risk of cardio-respiratory symptoms and CHD mortality among residents, aged 45-64 years, in two western Scottish towns between 1972 and 1976 (preliminary results were presented by Gillis *et al.*, 1984). With about an 80% response rate, 15,399 residents completed a standardized self-administered questionnaire on smoking habits, other lifestyle factors, and symptoms of respiratory and cardiovascular disease. By identifying couples living in the same household, the effect of exposure to ETS was investigated in a subsample of 3960 men and 4037 women. Eleven percent of the males (n = 428) and 12% of the females (n = 489) were lifetime nonsmokers and their cohabitants were also nonsmokers; they served as controls. Six percent of the males (n = 243) and 32% of the females (n = 1295) were passive smokers, *i.e.*, the case had never smoked but his or her cohabitant smoked. Thirty-six percent of the males (n = 1420) and 8% of the females (n = 323) were active smokers or exsmokers and had lived with a cohabitant who never smoked. Forty-seven percent of the males (n = 1869) and 48% of the females (n = 1922) were active smokers and their cohabitants also smoked. Through a national registry system, incidence of cancer and mortality was followed for 11.5 years (Hole *et al.*, 1989).

The cohort consisted of the 917 (428 men and 489 women) controls and the 1538 passive smokers (243 men and 1295 women). Passive smokers compared to controls did not differ in self-reported prevalence of angina (age- and sex-adjusted RR=1.02) and the relative risk estimate was not significantly changed (RR=1.11, 95% CI= 0.73 - 1.70) after adjusting for potential confounders including age, sex, social class, diastolic blood pressure, serum cholesterol, and body mass index. Controls and passive smokers also did not differ in self-reported prevalence of major abnormalities found on electrocardiogram; the age- and sex-adjusted relative risk was 1.10 which increased to 1.27 (95% CI=0.48 - 3.35) after adjusting for potential confounders. The effect of passive smoking was more apparent for fatal CHD events. Passive smokers experienced a higher age- and sex-adjusted mortality rate of CHD (47.4 per 10,000) than controls (27.3 per 10,000) (crude RR=1.74). The relative risk was statistically significant when the analysis was adjusted for the potential confounders mentioned above (RR= 2.01, 95% CI=1.21 - 3.35).

Among female subjects, the relationship between ETS exposure and risk of various CHD endpoints was evaluated by intensity of ETS exposure, defined as 'low' if their cohabitants smoked <15 cigarettes/day and 'high' if they smoked $\geq$15 cigarettes/day. There was no suggestion of increasing risk of abnormalities on electrocardiogram with increasing intensity of exposure. However, the risk for angina was elevated (RR=1.61) for those more highly exposed to ETS smoking. A trend of increasing risk with increasing level of ETS exposure was most apparent for fatal CHD events. Compared to women with no exposure, the relative risk was 2.09

for women with low ETS exposure and 4.12 for women with high ETS exposure (no confidence limits were provided).

Although history of angina and abnormalities on the electrocardiogram were based on self-reports, results were believable since the risks associated with ETS and active smoking were stronger for fatal cardiovascular events than for nonfatal events or symptoms of disease. Risk for angina (adjusted for age and sex) increased 2% for passive smokers, 67% for active smokers living with nonsmokers, and 98% for active smokers living with smokers compared to controls. The corresponding increase in risk for abnormalities on the electrocardiogram was 10%, 40% and 50%, respectively. Compared to controls, risk of death due to CHD increased 75% for passive smokers, 123% for active smokers living with a nonsmoker, and 122% for active smokers living with another smoker (*i.e.*, exposed to ETS). Thus, this study demonstrates that ETS exposure may have considerable effect on risk of both cardiovascular symptoms and CHD death, with a stronger effect for fatal CHD events.

An advantage of this prospective study is that it covered the entire population of men and women aged 45-64 years in two towns. In addition, information on other risk factors for heart disease is available for adjustment in the analysis. Unlike most studies in which smoking habits of spouses were obtained from the nonsmokers under study, the cohabitees (most of whom were spouses) directly provided information regarding their smoking habits, reducing the possibility of misclassification.

Evans County, Georgia *(Humble et al., 1990)*

The association between ETS exposure and CHD mortality was investigated among nonsmoking women living in Evans County, Georgia (Humble *et al.*, 1990). In 1960-61, 92 percent of all residents aged 40-74 years in this rural county participated in a cardiovascular disease study that included complete physical examinations and an interview on demographic and medical history. At enrollment, there was a total of 1,127 women, of whom 943 (554 white, 389 black) reported they had never smoked. The analysis on ETS was restricted to 513 women (328 white, 185 black) who were married to never smokers or current smokers at baseline. The authors excluded nonsmoking women married to exsmokers in the analysis on the basis that there may be more misclassification of the smoking habits of index subjects and their husbands if they were exsmokers. Vital status was determined on May 1, 1980. All mortality due to circulatory diseases (i.e., including strokes) (codes 390-456, ICD 8th Revision) listed as an underlying cause of death on the death certificates were considered in this analysis.

Results on ETS exposure were presented for all subjects combined, and separately by race and social class. The social class index was based on the occupation, education, and income of the head of household, applicable for rural settings. Nonsmoking women married to current smokers showed higher risks for all CHD mortality than women married to never smokers. For all subjects combined, the age-adjusted relative risk for all CHD mortality was 1.34. A higher relative risk value was obtained after adjusting for potential confounders including age, diastolic blood pressure, total serum cholesterol, and body mass index (RR=1.59, 95% CI=0.99 - 2.57). The increased risk was observed for all black women (adjusted RR=1.78, 95% CI=0.86 - 3.71)

and for white women of high social class (adjusted RR=1.97, 95% CI=0.72 - 5.34), but not for white women of low social class (adjusted RR=0.79, 95% CI=0.32 - 1.96).

There are no obvious explanations for the inconsistent finding between white women of different social classes. However, the number of CHD deaths by race and social class were not presented. Subgroup analysis based on small numbers may have produced unstable risk estimates. The authors stated that results were similar for all CHD and for smoking-related CHD, without describing which diseases included under all CHD would be excluded under smoking-related CHD.

This study presented data on subjects' smoking habits at enrollment and at a later time, providing an assessment of the stability of smoking habits in index subjects as well as in their spouses. Comparison of subjects' smoking status in 1960 and 1967 showed that 98 percent of nonsmoking women again reported that they never smoked in 1967. Similarly, an equal percent of never smoking husbands maintained their nonsmoking status in 1967, while 25 percent of husbands who smoked in 1960 described themselves as nonsmokers in 1967. This suggests that some husbands who were exsmokers at baseline might have reported themselves to be lifetime nonsmokers. Although no details were provided regarding how the questions were asked, they are presumed to have been asked in the same way in 1960 and in 1967. These results suggest it is not likely that an index subject or spouse who was a nonsmoker at baseline became a smoker whereas some smokers at baseline would be expected to have stopped smoking over time.

California Seventh Day Adventists *(Butler, 1988)* (Dissertation - unpublished)

A large cohort study of Seventh-Day Adventists (SDAs) in California was initiated in 1974 and was designed to investigate the association of lifestyle and nutritional factors with morbidity and mortality. A basic demographic questionnaire containing a question on smoking status was sent to all registered Adventist households with a 58% response rate. To examine the role of ETS exposure in this population, two analyses were conducted. One analysis was based on some 11,000 married couples (referred to as the spouse pairs cohort). A second analysis involved 6,467 subjects (referred to as the AHSMOG cohort) who were participants in an air pollution study.

The cohort was followed between 1976 to 1982 for cancer incidence and mortality. Incidence of cancer was based on responses to a questionnaire which was sent annually to all cohort subjects and asked about hospitalizations in the past year. Medical records relating to reported hospitalizations were then reviewed. Mortality rates were determined via linkage with the California Death Files and National Death Index Systems, and reviewing all deaths entered in church records. Death certificates were obtained on all reported fatalities, and information on underlying and contributing causes of death was abstracted.

The definition of ETS exposure differed for the spouse pair cohort and for the AHSMOG cohort. In the spouse pair cohort, ETS exposure was based on the husbands' smoking status at the time of marriage. However, this measure of ETS exposure was crude since subjects were not asked specifically when they started or stopped smoking. A married woman was classified as not exposed if her spouse was a never smoker or if the spouse's age at marriage equaled or was greater than his age of baptism. This is based on the assumption that the age of baptism was the

latest age at which a baptized SDA adult stopped smoking since smoking is a church proscription. On the other hand, a married woman was classified as exposed to ETS if her spouse was a current smoker, or if her spouse was an exsmoker who was not a baptized SDA, or if the spouse's age of baptism was greater than his age at marriage. In the AHSMOG cohort, specific questions were asked about ETS exposure including the number of years a subject lived or worked with a smoker.

In the spouse pair cohort, there were a total of 9785 nonsmoking women; of these, 7246 were married to nonsmokers and 2309 to smokers (in 230 subjects, the smoking status of the husband was not known). Based on 87 CHD deaths in nonsmoking women, those married to exsmokers did not show any elevation in risk (age adjusted RR=0.96, 95% CI=0.66-1.66) compared to nonsmoking women married to nonsmokers. However, there was some suggestion of an increased risk for nonsmoking women married to smokers (age adjusted RR=1.40, 95% CI=0.51-3.84). The increased risk observed among nonsmokers married to current smokers was based on only four CHD deaths. It is presumed that current exposure in this context means that the spouse was a current smoker and not a past smoker.

In the AHSMOG cohort, there were a total of 70 female deaths and 76 male deaths from CHD occurring among never smokers during the period of follow-up. Living with a smoking spouse was not associated with an increased risk of CHD in men but was associated with an increased risk of CHD in women. Compared to women who did not live with a smoker, those who lived with a smoker for 1-10 years or 11+ years showed adjusted RRs of 1.46 (95% CI=0.7-3.1) and 1.53 (95% CI=0.9-2.5), respectively (p for trend = 0.21). Years of working with a smoker was also not associated with risk of CHD in men but was associated with an increased risk of CHD in women, after adjusting for age. The relative risks for years working with a smoker changed from less than 1.0 in unadjusted analysis to close to 2.0 when the analyses were adjusted for age (Table 8.1).

Thus, the evidence from the spouse pair cohort and the AHSMOG cohort suggest that exposure to ETS at home and at work increased the risk of heart disease mortality in nonsmoking women but not in nonsmoking men. The effect of ETS exposure from work was of borderline statistical significance. There are no apparent reasons for the difference in results by gender. Although ETS exposure in the spouse pair cohort is derived by comparing the surrogate measure for smoking cessation (age at Baptism) to the age at marriage, the extent of misclassification of ETS exposure can be evaluated in a subset of women who responded to specific questions on spouses' smoking in the AHSMOG cohort and were included in the spouse pair cohort. There was an agreement in classification by ETS exposure in 86% of subjects included in both cohorts. However, 5.9% of the women responded they were not exposed to spouses' smoking in the AHSMOG cohort but were classified as exposed in the spouse pair cohort, and 5.8% who responded that their spouse smoked were classified as not exposed.

CPS I and CPS II *(LeVois and Layard, 1995)*

The analysis by LeVois and Layard (1995) utilized data from the American Cancer Society CPS I and CPS II studies. In brief, the CPS I study included more than one million men and women who were enrolled in 1959-1960. This analysis was based on 13 years of follow-up (1960-1972).

Follow-up was 92.7% complete. The CPS II study included approximately 1.2 million subjects who were enrolled in 1982. For this analysis, the cohort was followed for 6 years (1983-1988). Vital status was ascertained for 98.2% of the cohort, and death certificates were obtained for 94% of decendents. Both CPS I and CPS II collected data on smoking habits including the number of cigarettes smoked per day. Only self-reported never-smokers who had spouses with known smoking habits were included in these analyses. Each spouse was categorized as a nonsmoker, former smoker or smoker of 1-19, 20-39, and 40 or more cigarettes per day.

In the CPS I cohort there was a total of 88,458 male and 267,412 female never-smokers with spouses having known smoking habits. After 13 years of follow-up, there were 7758 CHD deaths in men and 7133 CHD deaths in women. As discussed in more detail below, a major limitation of the LeVois and Layard analysis of these data is the lack of clarity on selection of subjects for analysis and inconsistency in their reporting of the results.

In CPS I, the age- and race-adjusted RR for CHD mortality associated with any ETS exposure from spouses was 0.97 (95% CI=0.90, 1.05) in men and 1.03 (95% CI=0.98, 1.08) in women. Results were unchanged when the amount smoked by spouses was considered. For men whose wives smoked 1-19, 20-39, and 40 or more cigarettes per day, the RRs for CHD mortality were 0.99, 0.98, and 0.74, respectively. For women whose husbands smoked 1-19, 20-39, and 40 or more cigarettes per day, the RRs for CHD mortality were 1.04, 1.06, and 0.96, respectively. Nonsmoking men and women whose spouses were former smokers showed risks for CHD that were close to 1.0 (Table 8.1).

In the CPS-II cohort, among a total of 108,772 male and 226,067 female never-smokers with spouses having known smoking habits, there were 1966 CHD deaths in men and 1099 CHD deaths in women. After adjusting for age and race, there was no association between any ETS exposure from spouses and risk of CHD mortality in men (RR=0.97, 95% CI=0.87, 1.08) or in women (RR=1.00, 95% CI=0.88, 1.14). However, in both men and women, there was some increase in risk when amount smoked by spouses was considered. The risk of CHD mortality among men who were never-smokers married to women who smoked 1-19, 20-39, and 40 or more cigarettes per day were 1.36, 1.28, and 1.13, respectively, compared to men married to nonsmokers (Table 8.1). The corresponding RRs in never-smoking women were 1.14, 0.98, and 1.27. However, never-smoking men married to women who were former smokers showed a significantly lower risk of CHD mortality (RR=0.81, 95% CI=0.70, 0.98). The RR for CHD mortality was 0.99 (95% CI=0.86, 1.13) for never-smoking women married to husbands who were former smokers.

LeVois and Layard (1995) combined the CPS I and CPS II studies and reported a significant decreased risk of CHD (RR=0.79, 95% CI=0.80, 0.97) in nonsmoking men married to wives who were former smokers. However, the value of the combined RR presented in the text (RR=0.88, 95% CI=0.79, 0.97; see pg 188 of LeVois and Layard (1995)) differed from the combined RR presented in table 4 (RR=0.79, 95% CI=0.80, 0.97; see pg 189 of LeVois and Layard (1995)). It is unclear which of the combined RRs is correct. The results obtained are inconsistent with those of Steenland *et al*. (1996); these investigators conducted a more complete analysis of the same data set (see below).

Although this study has the advantage that the results were based on the largest number of subjects and CHD events, LeVois and Layard (1995) presented few details about the subjects not included in the analysis. For example, it is unclear what percent of subjects were excluded in either study because their own smoking habits were missing or because the smoking habits of spouses were unknown. The investigators examined the effect of 'any' ETS exposure from spouses and exposure from former spouses but they did not investigate the effects of *any* ETS exposure from current smoking spouses. The significant finding these investigators emphasized was the reduction in risk among men married to exsmokers when results from the two CPS studies were combined; we question whether the combined RR is correct (see above).

As pointed out by Steenland *et al.* (1996) and Glantz and Parmley (1996), ETS exposure may have both acute and chronic effects on the heart. The emphasis of LeVois and Layard on 'any' (*i.e.*, current or former) ETS exposure from spouses and exposure from spouses who were former smokers strongly biased the results toward the null. First, results for 'any' exposure to spousal ETS diluted the effects associated with exposure to current smokers by including exsmokers. This is evident when one compares the RRs associated with any ETS exposure versus the RRs associated with amounts currently smoked by spouses (Table 4 of LeVois and Layard, 1995) (RRs associated with any current smoke exposure were not presented and could not be computed on the basis of the data presented). The RRs associated with any ETS exposure was less than 1.0 for men (RR=0.97) and close to 1.0 for women (RR=1.0 and 1.03) in the CPS I and CPS II analyses. However, almost all the RRs associated with each exposure category (based on amount currently smoked by spouses: 1-19, 20-39, 40+ cigarettes per day) were above 1.0 for women in both CPS I and CPS II and for men in CPS II. In fact, in the CPS II analysis, five of the six RRs associated with varying amounts smoked by spouses were above 1.13. These RRs by amounts currently smoked by spouses suggest that the RR for any exposure to current smokers is above 1.0. Second, the effect of exposure from former smokers may be negligible, similar to the rapid reduction in heart disease risk seen among active smokers upon cessation of smoking.

CPS-II Cohort *(Steenland et al., 1996)*

The analysis by Steenland *et al.* (1996) utilized data from the CPS-II cohort based on 7 years of follow-up. The original CPS-II cohort consisted of 1,185,102 men and women who were enrolled in 1982. By December 1989, 91.2% (1,080,689) were alive, 8.6% (101,519) had died, and the remainder had unknown vital status. Including only participants who had never smoked, for whom information on marital status was available and whose spouses had classifiable smoking habits, there remained 353,180 women and 126,500 men. Death due to CHD was reported in 4911 women and 3251 men.

Results from four analyses were presented in this report. The first three analyses dealt specifically with ETS exposure from spouses, whereas the fourth analysis investigated the effects of ETS exposure at home, at work, and in other settings. The first analysis was conducted only among those married individuals with spouses also enrolled in the CPS-II study, and for whom there were valid dates of marriage and sufficient data on smoking cessation to indicate whether the spouses had smoked during marriage. Included in this analysis were 2494 CHD deaths in men and 1325 CHD deaths in women which had occurred in 101,277 men and 208,372 women after 7 years of followup. The second, third and fourth analyses utilized subsets of eligible subjects

derived from the first analysis. The second analysis was conducted only among those with single marriages and for whom information on amounts and duration of exposure to smoking during marriage were available. These restrictions led to 58,530 men and 99,821 women and a corresponding number of 1299 and 572 CHD deaths. The third analysis compared the risk of CHD among individuals who reported current exposure at home and were married to currently smoking spouses to those who reported no current ETS exposure at home and were married to never-smoking spouses. This analysis included 54,668 men with 1180 CHD deaths and 80,549 women with 426 CHD deaths. The fourth analysis was conducted on nonsmoking individuals who provided information regarding their exposure to ETS at home, at work, or in other social settings. This analysis was based on 1751 CHD deaths in some 76,710 men and 2403 deaths in 186,368 women (the number of subjects and CHD events were lower in the analyses on ETS exposure at work or in other social settings). Each of the four analyses adjusted for variables including age, self-reported history of heart disease and use of heart disease medication, self-reported history of hypertension, diabetes or arthritis, body mass index, education, use of aspirin, diuretics or estrogens (women only), alcohol use, employment history and exercise.

Small increased risks for CHD mortality in men and women in association with current exposure to spouses' smoking were found in each of the analyses (analyses 1 to 3, Table 8.1). In the first analysis, nonsmoking men exposed to currently smoking wives showed a RR of 1.22 (95% CI= 1.07, 1.40) for CHD mortality whereas nonsmoking women exposed to currently smoking husbands showed a RR of 1.10 (95% CI=0.96, 1.27). These RRs were strengthened slightly when the analyses were restricted to spouses with single marriages (analysis 2). The RR was 1.48 (95% CI=1.21, 1.80) in men and 1.18 (95% CI=0.91, 1.46) in women. An increased RR associated with exposure to a currently smoking spouse was also observed in the third analysis, in which self-reported exposure to ETS concurred with the spouses' reporting of their tobacco use (analysis 3). In this analysis, the RR for CHD mortality in association with currently smoking spouses was 1.23 (95% CI=1.03-1.47) in nonsmoking men and 1.19 (95% CI=0.97-1.45) in nonsmoking women. There was, however, no association between risk of CHD mortality in nonsmoking men and women and being married to spouses who were former smokers (analyses 1 and 2, Table 8.1).

Dose-response relationships in terms of amounts smoked by spouses, duration of ETS exposure, and pack years of ETS exposure were evaluated. There was no evidence of a smooth trend of increasing risk with increasing number of cigarettes smoked by spouses (analyses 1 and 3, Table 8.1) or with increasing pack years of ETS exposure (analysis 3, Table 8.1). There was some suggestion of a trend of increasing risk of CHD mortality in nonsmoking men and women with increasing number of years exposed to spouses' smoking (analysis 2, Table 8.1).

The fourth analysis examined the association between risk of CHD mortality and exposure to ETS exposure at home, at work, and in other settings. Small elevated risks were associated with all sources of ETS exposure, although only the association between CHD risk in nonsmoking men and ETS exposure at home was statistically significant (Table 8.1).

Analyses were also presented separately for subjects aged <65 at baseline and for individuals with a history of heart disease and those without a history of heart disease. Nonsmoking subjects who were aged <65 at study entry showed a slightly higher increased risk of CHD

mortality in relation to exposure to currently smoking spouses. For example, nonsmoking men aged <65 at baseline who were married to currently smoking women showed a RR of 1.33 for CHD mortality (this RR was 1.22 for all nonsmoking men). There is also some suggestion that the risk of CHD mortality associated with exposure to a smoking spouse was more apparent in individuals who had heart disease at baseline. For example, the risk of CHD mortality in nonsmoking men associated with exposure to wives who were current smokers was 1.18 (95% CI=0.98, 1.41) among those who had no history of heart disease at baseline and 1.24 (95% CI=1.01, 1.53) among those who had a history of heart disease at baseline.

The differences in findings in this study and those reported by LeVois and Layard (1995) are noteworthy given that both analyses utilized data from the CPS II study. The size of the relevant study population and the number of CHD deaths included by Steenland *et al.* (1996) differed from those included by LeVois and Layard (1995). In contrast to the detailed description of the inclusion and exclusion criteria presented by Steenland *et al.* (1996), LeVois and Layard (1995) provided few details regarding their study methods. Differences in the follow-up period, in the definition of spousal smoking or other criteria for inclusion and exclusion may have contributed to the differences in these two reports. The analytic methods used in the two studies also differed. Steenland *et al.* (1996) investigated separately the effects of current and former exposure to ETS from spouses, whereas LeVois and Layard (1995) examined the effects of any spousal ETS exposure. Given that there is little evidence of an increased risk associated with being married to former smokers, LeVois and Layard's (1995) analysis of any spousal exposure to ETS may have diluted the effects of current exposure to spousal smoking on CHD mortality in nonsmokers.

Nurses' Health Study *(Kawachi et al., 1997)*

Kawachi *et al.* (1997) investigated the association between exposure to ETS and risk of CHD using the Nurses' Health Study, a cohort which was established in 1976 and included 121,700 female nurses in the U.S. A self-administered baseline questionnaire was completed by study participants which included information on active smoking history and a large number of lifestyle and dietary factors. Follow-up questionnaires have been completed by participants every two years to update information on cardiovascular disease risk factors and the occurrence of major illnesses. In the 1982 follow-up questionnaire, questions related to exposure of ETS were asked. Specifically, two questions were asked to assess current ETS exposure at home and at the workplace. Extent of exposure was categorized as none, occasional, and regular. In addition, subjects were asked the total number of years they had lived as an adult with someone who has smoked regularly.

This analysis comprised incident cases of nonfatal MI (n=127) and fatal CHD events (n=25) which occurred after the 1982 questionnaire but before June 1, 1992 among the 32,046 women who had never smoked and remained nonsmokers during the follow-up period (1982 to 1992). The CHD events were confirmed by review of medical records of death certificates by physicians who were blinded to exposure status. Risk estimates were calculated with adjustment for age and multiple risk factors which included alcohol intake, body mass index, history of hypertension, diabetes, hypercholesterolemia, menopausal study, use of hormone replacement and oral contraceptives, physical activity patterns, and relevant dietary factors.

Compared to nonexposed women, those reporting occasional exposure to ETS at home or work had a multivariate adjusted RR for total CHD of 1.56 (95% CI=0.93-2.68), while those reporting regular exposure had a RR of 1.97 (95% CI=1.11-3.28). In this study population, exposure to ETS was associated with increased risks of both nonfatal MI and fatal CHD events (Table 8.1). ETS exposure, both at work and at home, were associated with an increased risk of CHD. Among women exposed only at work, the multivariate RRs of total CHD were 1.49 (95% CI=0.71, 3.14) among those occasionally exposed and 1.92 (95% CI=0.88 to 4.18) among those regularly exposed to ETS. Among women exposed to ETS only at home, the corresponding RRs were 1.19 (95% CI=0.63, 2.23) and 2.11 (95% CI=1.03, 4.33). Self-reported duration of years lived with a smoker was also associated with an increased risk of incident CHD events although there was not a smooth trend of increasing risk with increasing years of exposure. The multivariate adjusted RRs associated with 1-9, 10-19, 20-29, and 30+ years compared to less than 1 year of exposure were 1.0, 1.19, 1.54, 1.11 and 1.58, respectively.

This study has several important strengths. This analysis was conducted using a cohort study that is widely accepted as one of the best designed and most well conducted prospective studies and has been an extremely valuable resource in identifying and elucidating causes of various disease endpoints. Because of the availability of a large number of lifestyle factors in this study, these analyses controlled for a large number of lifestyle and dietary factors that have been suggested to potentially confound the CHD-ETS association. Although there is some diminution in the RRs with adjustment of these potential confounders, the risks remained elevated and were statistically significant in many of the analyses. This cohort study also provided information on ETS exposure at home and at work, and showed clearly that risk of CHD is increased in association with ETS at home alone, at work alone, and for both exposures combined. Moreover, these investigators showed that the risks associated with ETS exposure in never smokers are quite compatible with the active smoking findings in this study population. Women who smoked 1 to 4 cigarettes per day had a RR for total CHD of 1.94 compared to all never-smokers; this RR was increased to 2.61 when the reference category was set to never-smokers not exposed to ETS. Thus, the RR of 1.97 among women regularly exposed to ETS at home or at work is not incompatible with the active smoking findings.

8.1.2 Case-control Studies

United Kingdom *(Lee et al., 1986)*

In a case-control study originally initiated to examine the relationship between types of cigarettes smoked and risk of lung cancer, chronic bronchitis, CHD, and stroke, Lee *et al.* (1986) evaluated the relationship between ETS exposure and these health outcomes. The original study began in 1977, and the questionnaire was modified in 1979 to assess ETS exposure for married patients in 4 of the 10 hospital regions included in the study. Controls were patients without one of the 4 diagnoses mentioned above; each control was individually matched to a case on sex, age, hospital region, and when possible, hospital ward and time of interview. A total of 507 (286 male, 221 female) currently married patients with CHD answered questions on ETS exposure. It is unclear whether these 507 subjects were nonsmokers since these numbers do not agree with subsequent numbers on CHD presented in the paper.

In one analysis, 118 subjects with CHD and 451 controls were compared in terms of whether his/her spouse smoked and the number of manufactured cigarettes smoked per day. Male CHD patients whose wives smoked during the entire marriage showed a relative risk of 1.24, but the association was absent for female patients (RR=0.93). In a second analysis, 66 CHD cases and 254 controls quantified their ETS exposure at each of four settings (home, work, during daily travel, and during leisure time) using a 4-point scale (score of 0 indicated no exposure, a score of 3 indicated heavy exposure). To obtain a combined index of ETS exposure, the scores for each setting were summed. There was no association between this combined index of ETS exposure and risk for CHD in men and women. The relative risks were 1.00, 0.52 and 0.61 for the combined indices of ETS exposure of 0-1, 2-4, and 5-12, respectively.

Results from this study and the conclusion of no association are questionable. Information on passive smoking was obtained on a subset of cases and controls, and the different analyses on ETS exposure included substantially different numbers of cases and controls. Thus selection bias of cases and controls who answered the questions on passive smoking cannot be excluded. In addition, information on potential confounders for CHD was not available.

China *(He et al., 1989)*

He *et al.* (1989) conducted a case-control study on ETS exposure and CHD in the Peoples' Republic of China which included 34 women with CHD and 68 controls (34 hospital-based, 34 population-based). Subjects were interviewed regarding their smoking habits and those of their husbands. Population controls were matched to cases on age, race, residence, and occupation, but it is unclear whether the matching criteria were applied to hospital controls. A significant, 3-fold increase in relative risk (95% CI=1.3-7.2) for CHD was observed for nonsmoking women whose husbands were smokers. The risks increased with increasing number of cigarettes smoked and with increasing duration of smoking by the husband. The relative risk associated with ETS exposure diminished substantially (RR=1.50, $p<0.01$) when other CHD risk factors (including personal and familial history of hypertension, familiar history of CHD, drinking, physical exercise, previous history of hyperlipidemia) were adjusted for in the analysis. Analysis by specific heart disease outcome showed a relative risk of 4.7 ($p <0.05$) for angina (n=21), and a relative risk of 2.5 ($p>0.05$) for MI (n=13) in relation to husbands' smoking.

There are several important limitations of this study. First, the study is small, based on 34 cases and 68 controls. Second, only partial information about the study methods was presented. The 34 CHD patients represented cases who were diagnosed by coronary arteriography or had MI during 1985-1987 in one hospital in Xian, China. The criteria for selecting these cases were not described and it is unclear what percent of cases diagnosed during the study period was selected. Furthermore, the types of patients included as hospital controls were not described. Some population controls had presumably taken the exercise electrocardiogram test, questioning whether they are truly representative population-controls. Thus, selection bias of cases and controls cannot be ruled out. It is also uncertain whether uniform methods were used to collect information from cases, hospital controls, and neighborhood controls.

The significant findings from the study must be interpreted with caution given these serious limitations in study methods. It is also questionable whether the point estimates for angina and MI separately are meaningful given these results were based on 21 and 13 cases respectively.

New South Wales, Australia *(Dobson et al., 1991a)*

A case-control study of ETS exposure and risk of heart attack and CHD death was conducted by Dobson *et al.* (1991a) in New South Wales, Australia. Cases were residents of the study area, aged 35-69 years who had a fatal or non-fatal definite or possible MI or a coronary death (with insufficient information for more specific classification) during the study period (July 1, 1988 to October 31, 1989). To ensure completeness of case ascertainment, the hospital morbidity data system and the official death records were compared. If more than one CHD event occurred during the study period, only the first event was included in the analysis. In addition to diagnostic information, data on medical history, cigarette smoking, and exposure to passive smoking at home and at work were obtained by an interview conducted by the study nurses while subjects were still in the hospital. For subjects who had died, the next-of-kin was contacted (the number of interviews conducted with the subjects themselves versus next-of-kin was not specified). Information on ETS exposure was missing for about 15% of all nonsmoking CHD patients because they had died and a next-of-kin interview could not be conducted. Controls had previously participated in a community-based risk prevalence study. For this study, they completed a self-administered questionnaire which covered demographic characteristics, smoking behavior and medical history. Controls were also asked to donate a blood sample and complete physical measurements. The participation rate among controls was 63% for all three components of the study, and 80% for the questionnaire interview.

The study included 183 male CHD patients who had never smoked and 336 who were exsmokers; the corresponding number of female CHD patients were 160 nonsmokers and 80 exsmokers. Male cases were compared to 293 male nonsmoker and 332 exsmoker controls, respectively, whereas female cases were compared to 532 female nonsmoker and 151 exsmoker controls. Controls were selected to match cases on age (between ages 35 to 69), but how closely cases and controls were age-matched was not specified.

The ETS effect was considered separately for nonsmokers and exsmokers after adjustment for age (in 5-year intervals), sex, and prior history of heart disease. Exposure to ETS at home was not associated with risk of heart attack in nonsmoking men (adjusted RR=0.97, 95% CI=0.50, 1.86) but was associated with an increased risk in nonsmoking women (adjusted RR=2.46, 95% CI=1.47, 4.13). Based on a small sample of nonsmokers who worked outside the home (75 male cases versus 205 male controls; 17 female cases versus 197 female controls), ETS exposure at work was not associated with risk of heart attack in men (RR=0.95, 95% CI=0.51, 1.78) or in women (RR=0.66, 95% CI=0.17, 2.62).

This case-control study has several methodologic deficiencies which may have biased the estimated effect of ETS on risk of heart disease in this study. The percent of nonsmoking male and female cases and controls who reported exposure to ETS at home was low in this study: 12.0% nonsmoking male cases and 11.6% nonsmoking male controls reported ETS exposure; the corresponding figures in females were 26.9% and 18.6%. The percentages of controls who

reported ETS exposure were 40-60% among controls in most lung cancer studies (U.S. EPA, 1992). Controls in this study were participants in a previous health survey, and may have been 'healthier' and thus were less likely to have had exposure to ETS. However, this reasoning does not explain the low prevalence of ETS exposure among cases. The precise questions on ETS exposure that were asked were not described (Dobson *et al.*, 1991a), limiting our ability to fully interpret these findings. In addition, different methods were used to obtain information from cases and controls. Whereas most cases were interviewed by nurses while they were in the hospital, controls completed a self-administered questionnaire. Information bias cannot be ruled out and the direction of bias cannot be determined. Lastly, potential confounders including other risk factors for heart disease and socioeconomic status were not available.

New Zealand *(Jackson et al., 1991; Jackson, 1989)* [unpublished dissertation]

Jackson *et al.* (1991) conducted a population-based case-control study of non-fatal MI and fatal heart disease in New Zealand. A population register identified nearly 99% of the CHD occurring in the study population, which included all white men and women aged 25-64 living in the Auckland statistical area between March 1986 and February 1988 who were also registered on the general electoral rolls. All patients with non-fatal MI requiring admission to a hospital were invited to participate. The next of kin of subjects who had died of CHD were also invited to participate. Controls were randomly selected from the study population by using the electoral rolls as the sampling frame. For each male and female case who was interviewed, approximately 1.5 male controls and 3 female controls were interviewed. Cases and controls were matched on respondent type (i.e., self-respondent versus next-of-kin respondent). This was achieved by using the controls for the subjects with MI (self-respondents) as controls also for those who had died of CHD by interviewing their next of kin about them (the self-respondent controls). The interviews asked about use of tobacco products, current drug treatment of hypertension, leisure time physical activity, and prevalence of angina. Questions on passive smoking were added during year 2 of the study. Specifically, questions were asked about tobacco smoke exposure from any cohabitant and at work.

The analysis on ETS exposure was limited to subjects with no history of MI or angina and were never smokers which included 28 male MI cases and 123 male controls, 21 male fatal CHD and 61 male controls, 11 female MI cases and 112 female controls, and 9 female fatal CHD and 62 female controls. The age- and social class adjusted OR for MI in relation to ETS exposure at home (and/or work) was 2.7 (0.57-12.3) in females and 1.03 (95% CI=0.27-3.9) in males. The adjusted OR for fatal CHD was 5.8 (95% CI=0.95-35.2) in women and 1.1 (95% CI=0.23-5.2) in men.

Although this study was part of a large case-control study of alcohol intake and risk of CHD conducted in collaboration with the World Health Organization MONICA project (Jackson *et al.*, 1991), questions on ETS exposure were added during year 2 of the study and were unpublished (Jackson, 1989 [unpublished dissertation]). Only a small number of nonsmokers were included in this analysis. Selection bias cannot be excluded since it is unclear what percent of never-smoker cases and controls answered questions on ETS exposure.

Italy *(La Vecchia et al., 1993)*

This Italian case-control study of acute MI was conducted in 1988-89 within the framework of the GISSI-2 study (a randomized clinical trial of alteplase versus streptokinase and heparin versus no heparin) which included 12,490 cases of acute MI (GISSI-2, 1990; Roncaglioni *et al.*, 1992). From the original study population, 113 cases of acute MI (44 women and 69 men aged 34-74) occurred in never smokers. Two hundred and twenty-five controls (60 women and 125 men, aged 29-74) were compared to the cases; controls were admitted to the same network of hospitals for acute diseases not related to any known or potential cardiovascular risk factors and were also never smokers. Exposure to passive smoking at home was based on spouse's smoking habits which included smoking status (never-smoker, exsmoker, current smoker), number of cigarettes smoked per day, number of years the couple had lived together (presumably as a measure of duration of ETS exposure), and the number of years the spouse had stopped smoking if he/she was a former smoker.

Compared to subjects married to never-smokers, the adjusted OR for acute MI associated with being married to exsmokers was 0.91 (95% CI=0.36-2.28) and the OR for those married to current smokers was 1.21 (95% CI=0.57-2.52). Gender, age, education, coffee consumption, body mass index, serum cholesterol, hypertension, diabetes, and family history of acute MI were adjusted for in the analysis. Among subjects married to current smokers, the risk was higher (RR= 1.30, 95% CI=0.50-3.40) among those whose spouses smoked 15 or more cigarettes per day than those who smoked less than 15 cigarettes per day (RR= 1.13, 95% CI=0.45-2.82).

This study has the advantage in that it was part of a large study in which some information on passive smoking, other heart disease risk factors and dietary factors were available. The dietary data from this study suggest that subjects who lived with a smoking spouse and those who lived with a nonsmoking spouse did not differ in the dietary intake of selected indicator foods.

Xian, China *(He et al., 1994)*

He *et al.* (1994) conducted a second case-control in Xian, China. Cases included 59 Chinese women with CHD and 126 controls; all subjects had full time jobs and had never smoked. Cases had non-fatal, incident CHD and were identified from one of three large teaching hospitals in the study area between December 1989 and November 1992. Three types of controls were interviewed, including patients admitted because of suspected CHD (these subjects were later found to be free of CHD)(n=26), other hospital controls (n=65), and a random sample of healthy subjects identified from a community screening program (n=35).

In-person interviews were conducted with cases and controls using a structured questionnaire which collected information on demographic characteristics, history of hypertension, hyperlipidaemia and diabetes mellitus, family history, history of smoking and passive smoke exposure from husbands and at work, drinking history and exercise.

There were no significant differences between cases and controls in age, marital status, occupation, or education although a higher percentage of cases were over age 55, were not married, were factory workers and had fewer than 9 years of education. Risk of CHD was significantly increased in relation to ETS exposure from husbands (defined as living with a

smoking husband for over 5 years) (crude OR=2.12, 95% CI=1.06-4.25) and at work (defined as working with smoking coworkers for over 5 years) (crude OR=2.45, 95% CI=1.23, 4.88). Crude analysis showed that when ETS exposure from husbands and at work were considered jointly, the risks increased approximately 2-fold for ETS exposure from husbands only and at work only, and by 4-fold for exposures both at work and from husbands. Although the ORs in relation to passive smoke exposure from husbands (adjusted OR=1.24, 95% CI=0.56-2.72) and at work (adjusted OR=1.85, 95% CI=0.86-4.00) were subtantially reduced after adjustment for other risk factors for CHD (age, history of hypertension, type A personality, total cholesterol, high density lipoprotein), the adjusted OR for any passive smoke exposure (from husband and/or work) remained statistically significant (adjusted OR=2.36, 95% CI=1.01-5.55). There were also significant trends of increasing risks with increasing intensity (amount smoked daily, number of smokers) and duration (in years) of ETS exposure at work (Table 8.2).

The main limitation of this study is the modest sample size of cases and controls and the fact that prevalent CHD cases may have been included. However, this study has the advantage of detailed information on ETS exposure at home and at work and on other heart disease factors, and adjustment of the analyses on ETS exposure for other potential confounding factors. Moreover, the opportunity to examine the role of ETS exposure at work was maximized given that all subjects worked full time. This study also attempted to assess the extent of information bias in several ways. First, there is no evidence of selective recall bias for being a patient with CHD: ETS exposure among controls who were initially suspected of CHD but were later found to be free of CHD by coronary arteriography (n=26) was similar to the ETS exposure experience of other hospital controls (n=65). Second, there was high concordance (over 70%) in responses regarding passive smoke exposure. Some 30% of subjects were interviewed a second time by a different interviewer who was blinded to the case-control status of the subject. Some of the husbands were also interviewed directly to validate the passive smoking information provided by their wives.

National Mortality Followback Survey *(Layard, 1995)*

Layard (1995) conducted a case-control analysis to examine the association between CHD mortality and spousal cigarette smoking using data on never-smoking decedents from the 1986 National Mortality Followback Survey, which was conducted in 1986 by the U.S. National Center for Health Statistics. The survey was based on a national probability sample of about 1% of all deaths in 1986 of U.S. residents aged 25 years or older.

This analysis included all deaths due to CHD (ICDO 9, codes 410-414) among males aged 25-44 years and females aged 25-54 years who were reported by next of kin to be lifetime never-smokers (i.e., had smoked fewer than 100 cigarettes in their entire lives). Decendents were excluded from the analysis if they had never married, their marital status was unknown, or the smoking history of their spouses was unknown (549 males and 692 females subjects were excluded from the analysis for these reasons). After these exclusions the case group included 1389 (475 males and 914 females) CHD deaths. Controls (996 males and 1930 females) were selected from the same study population from those whose causes of death were considered to be non-smoking related. However, the actual causes of death among controls were not presented. Next of kin of both cases and controls completed a mailed questionnaire which provided

information on demographic characteristics, dietary patterns, cigarette smoking habits of index subject and their spouses, alcohol use, education, income, and history of other diseases.

In this study, there was no association between exposure to spouse's smoking and risk of CHD death in men (OR=0.97, 95% CI=0.73-1.28) or in women (OR=0.99, 95% CI=0.84-1.16). Analysis by amount smoked by spouses (<15, 15-34, 35+ cigarettes/day) also did not reveal any association between amount smoked by the spouses and risk of CHD mortality. These results were unchanged after adjustment for potential confounders which included dietary factors, relative weight, history of diabetes or hypertension, family history of heart attack. education and family income.

It is, however, difficult to interpret these results. First, it appears that the controls were not matched to cases on age at death or race since the mean age at death for cases were significantly older (72.6 years of age in men and 78.2 in women) than those for controls (64.8 years of age in men and 71.9 in women). The percent of white cases (74.9% in males, 73.9% in females) was also significantly higher than that in the control group (68.2% in males, 68.4% in females). Although the OR was adjusted for age, the specific type of age adjustment used was not described. Broad age groups used in age adjustment may not be adequate. Furthermore, the study was supposed to include all deaths among males aged 25-44 years and females aged 25-54 years but the mean ages of male cases were considerably older. The reason for this discrepancy was not explained. Moreover, since the actual causes of death among controls were not presented, whether their causes of death may be related to tobacco smoke exposure cannot be ascertained.

Muscat and Wynder (1995)

Muscat and Wynder (1995) conducted a hospital-based case-control study between 1980 and 1990 in four U.S. cities to evaluate the association between exposure to ETS during childhood and adult life and the risk of MI. Cases were newly diagnosed incident cases with MI who were admitted to teaching hospitals in New York, Philadelphia, Chicago and Detriot. Controls were patients who did not have heart disease and were hospitalized for conditions unrelated to tobacco use. Controls were frequency matched to cases on the basis of age ($\pm$ 5 years), race, and year of diagnosis. Ninety per cent of both eligible cases and controls were interviewed. Only patients who reported never smoking cigarettes were included in this analysis.

A standardized questionnaire was administered to all subjects in the hospital by trained interviewers. Subjects who smoked one or less than one tobacco product per day for 12 or fewer months were considered as never smokers. An extensive series of questions were asked regarding exposure to ETS. These questions included childhood exposure, adult exposure, exposure to other people's smoke at work and on any form of transportation. Each set of questions included identifying all sources of exposure (e.g. mother, father, spouse, children, other relative and roomers)and the duration of exposure in years.

A total of 114 cases (68 males and 46 females) and 158 controls (108 males and 50 females) were interviewed. Cases were somewhat older than controls (55.7 years for male cases versus 52.4 years for male controls; 58.7 years for female cases versus 57.9 years for female controls). Adult ETS exposure was associated with an elevated risk of MI in men (crude OR=1.3, 95% CI=0.7-2.4) and in women (crude OR=1.7, 95% CI=0.7-3.7). The OR was 1.5 (95% CI=0.9-2.6)

for men and women combined after adjustment for gender, age, education, and hypertension. There was, however, no smooth trend of increasing risk with increasing duration (1-20, 21-30, 31+ years) or pack-years (1-10, 11+ pack-years) of ETS exposure in adult life, although all the ORs were greater than 1.0 (see Table 8.2). Exposure to ETS at work was associated with a small increased risk in men (OR=1.2, 95% CI=0.6-2.2) but not in women (OR=1.0, 95% CI=0.4-2.5) whereas exposure to ETS in transportation was associated with an increased risk in women (OR=2.6, 95% CI=0.9-8.0) but not in men (this OR was not presented). In both men and women, there was no association between exposure to ETS during childhood and risk of MI.

8.2 Discussion of Epidemiologic Studies

To date there are 18 studies (ten cohort studies, eight case-control studies) which have examined the association between ETS exposure and risk of CHD. In 15 studies (nine cohort studies, six case-control studies) there was some suggestion of a small increased risk of CHD associated with ETS exposure. This result was statistically significant in six studies (Hirayama, 1984; Helsing *et al.*, 1988; Hole *et al.*, 1989; He *et al.*, 1989; He *et al.*, 1994; Kawachi *et al.*, 1997) and in one gender group in two studies (Dobson *et al.*, 1991a; Steenland *et al.*, 1996). A statistically nonsignificant increased risk was observed in the other seven studies, most of which had modest sample sizes (Jackson, 1989; Muscat and Wynder, 1995; La Vecchia *et al.*, 1993; Humble *et al.*, 1990; Helsing *et al.*, 1988; Garland *et al.*, 1985; Butler, 1988). Two (Layard, 1995; LeVois and Layard, 1995) of the three studies (Lee *et al.*, 1986; Layard, 1995; LeVois and Layard, 1995) which did not find an association between ETS exposure and risk of CHD were, in fact, very large studies. However, these three studies had other methodologic limitations. First, all three studies investigated the association between CHD risk and exposure to any smoking spouse (i.e., including former smokers) when there is some suggestion that only current exposure to ETS may influence the risk of CHD (see below). The suitability of the control group and the quality of information on ETS exposure are questionable in the large case-control study conducted by Layard (1995). This study relied exclusively on information provided by the next-of-kin of subjects who died of CHD or other causes and the completeness of the information is debatable. Moreover, causes of death among the controls were not presented. Thus selection bias of controls and misclassification bias of ETS exposure cannot be ruled out in this study. Third, LeVois and Layard (1995) combined the data from the CPS I and CPS II studies and found a significant reduced risk of CHD associated with exposure to spouses who were former smokers. This RR from the combined dataset is due mainly to a reduced risk (RR=0.81) in nonsmoking men associated with wives who were former smokers in the CPS II study. In Steenland's analysis (1996) of the CPS II study, the RR in nonsmoking men associated with wives who were former smokers was 0.99. Reasons for the discrepancy in study results between the two analyses of the CPS II study are not apparent. However, as noted above, Steenland *et al.* (1996) conducted a more thorough and comprehensive analysis of the same data set. Moreover, the results reported by Steenland *et al.* (1996) were more credible because increased risks were observed in multiple analyses which used different criteria to define eligible subjects. Increased risks were also observed in the analysis which was restricted to subjects who were concordant for self-reported current exposure to smoking and spousal reporting of current smoking.

A strength of these collective data which support an association between risk of CHD and exposure to ETS is that nine of the 15 studies were prospective studies (Hirayama *et al.*, 1984;

Garland *et al.*, 1985; Svendson *et al.*, 1987; Butler, 1988; Helsing *et al.*, 1988; Hole *et al.*, 1989; Humble *et al.*, 1990; Steenland *et al.*, 1996; Kawachi *et al.*, 1997). The cohorts were diverse and included high risk men (Svendson *et al.*, 1987), subjects in an affluent community (Garland *et al.*, 1985), lower risk subjects in a rural community (Humble *et al.*, 1990), Seventh Day Adventists (Butler, 1988), nurses in the U.S. (Kawachi *et al.*, 1997) and the general population in the U.S. (Helsing *et al.*, 1988; Steenland *et al.*, 1996), the UK (Hole *et al.*, 1990), and Japan (Hirayama, 1981, 1984, 1990). Although the sample sizes of some of the cohort studies were modest (Svendson *et al.*, 1987; Butler, 1988; Hole *et al.*, 1989; Humble *et al.*, 1990; Garland *et al.*, 1985), the analysis based on the CPS II study (Steenland *et al.*, 1996) included some 3000 CHD deaths. Almost all of the case-control studies were also relatively small (He *et al.*, 1989; Dobson *et al.*, 1991a; La Vecchia *et al.*, 1993; He *et al.*, 1994; Muscat and Wynder, 1995; Jackson, 1989) but these studies had an advantage in that specific questions on different sources of ETS exposure were asked and that almost all the cases and controls were interviewed directly regarding their ETS exposure. Although the case-control study conducted by Layard (1995) was large, information on ETS exposure may be less complete and was obtained exclusively from next-of-kin.

Misclassification of ETS exposure is a concern in examining these studies. Almost all the studies used spousal smoking as a measure of ETS exposure, while a few studies included questions on ETS exposure from other settings (see below). Because of the small sample sizes in some studies or because of the way information on smoking was originally obtained, some studies described spousal smoking as 'yes' or 'no'' (Svendson *et al.*, 1987, Hole *et al.*, 1989, Humble *et al.*, 1990, Lee *et al.*, 1986, Dobson *et al.*, 1991a, He *et al.*, 1989) without distinguishing whether spouses were exsmokers or current smokers. In studies of active smoking and heart disease, risk of heart disease decreases rapidly upon cessation of smoking, although there is still some residual risk of CHD attributable to past smoking (U.S. DHHS, 1990). Thus, any increased risk of heart disease in nonsmokers in relation to living with a spouse who is an exsmoker needs to be interpreted cautiously. A spouse who was an exsmoker at study enrollment may have resumed smoking during the period of follow-up. As a different possibility, an exsmoker spouse may have been a very heavy smoker with the non-smoking spouse heavily exposed, and the subsequent increased risk observed would be a residual effect of intense previous exposure. Alternatively, subjects married to exsmokers may be at an increased risk for CHD because of other characteristics in their lifestyles that are also associated with an increased risk of heart disease.

A few studies have provided information on the risk of CHD in association with ETS exposure from exsmoking spouses (Garland *et al.*, 1985; Butler, 1988; La Vecchia *et al.*, 1993; LeVois and Layard, 1995; Steenland *et al.*, 1996). In one study, nonsmokers married to former smokers and those married to current smokers both showed increases in risk of CHD compared to nonsmokers married to nonsmokers (Garland *et al.*, 1995). In three other studies (Butler, 1988; La Vecchia *et al.*, 1993; Steenland *et al.*, 1996), an increased risk of CHD was found in association with exposure to spouses who were current smokers but not with exposure to spouses who were former smokers. In one study (LeVois and Layard, 1995), a lower risk of CHD was found in association with exposure to spouses who were former smokers. The association between risk of CHD and exposure to spouses who were current smokers was not evaluated in this study.

Information on a dose-reponse relationship between exposure to spousal smoking and risk of CHD was available in several studies. A trend of increasing risk with increasing amounts smoked by spouses was suggested in four studies (Hirayama, 1984; He *et al.* , 1989; La Vecchia *et al.*, 1993; Kawachi *et al.*, 1997). However, in other studies, there is little evidence of a smooth trend of increasing risk with increasing amounts smoked by spouses (Helsing *et al.*, 1988; Steenland *et al.*, 1996; Muscat and Wynder, 1995) or with increasing duration of ETS exposure (Steenland *et al.*, 1996; Butler, 1988).

An advantage of the cohort studies is that information bias was largely avoided because information on the smoking status of index subjects and their spouses or other sources of ETS exposure was collected at study enrollment, prior to their illness or death. However, cohort studies are susceptible to misclassification resulting from cessation or resumption of smoking by spouses or family members. In one study which compared smoking habits at baseline and at some later time, there was a high concordance in the nonsmoking status of the index subjects (98%) and of their spouses (98%) over a 20 year period, although some 25% of spouses who were smokers in 1960 reported they had stopped smoking by the late 1960's (Humble *et al.*, 1990). This suggests that misclassification of nonsmokers (i.e., nonsmokers who became smokers) is probably minimal, but that exposure to smoking of spouses or other household members at enrollment may be higher than exposures in follow-up years. Thus, in studies with a relatively long follow-up period without reassessment of the smoking status (Hirayama, 1981; Humble *et al.*, 1990) the reported risk estimates may be associated with spouses' smoking for only part of the follow-up period, suggesting that the risk estimates associated with spouses who smoked during the entire follow-up period may be even higher.

The inclusion of smokers who claimed to be nonsmokers at study enrollment produces an upward bias in the observed relative risk for CHD from ETS exposure (Lee, 1989). The basis for this argument is the smoking concordance between husband and wife, i.e., a smoker is more likely than a nonsmoker to have been married to a smoker (Sutton, 1981). Consequently, an active smoker misclassified as a nonsmoker is more likely than a true nonsmoker to have had exposure to ETS, i.e., by being married to a smoker. Smoking causes heart disease, and thus a misclassified smoker has a greater chance of having heart disease than a nonsmoker. The net effect is that an observed association between ETS exposure and CHD among people who claim to be never-smokers may be partially explained by current or former active smoking by some of them. However, the extent of misclassification of smokers as nonsmokers in these studies is not known, but is likely to be small.

Two studies provided information on the effect of ETS exposure among exsmokers. These results differed, probably because exsmokers are a heterogenous group of individuals who stopped smoking for different reasons. Exsmokers who have given up smoking because of heart disease and other health problems may be more likely to avoid other smokers. In the study by Svendsen *et al.* (1987), the risks for CHD death, and for fatal and nonfatal CHD combined in relation to ETS exposure, were substantially weaker in the analysis including exsmokers than that conducted among never smokers only, suggesting a relatively weak ETS effect in exsmokers. On the other hand, in the case-control study conducted by Dobson *et al.* (1991a), the ETS effect was stronger in men who were exsmokers than nonsmokers, but this was not true in women.

Results from these studies suggest that there is not a consistent direction of upward bias if some exsmokers had misclassified themselves as nonsmokers at baseline.

Information on risk of CHD in relation to ETS exposure from workplace or other settings is available in a few studies (Butler, 1988; Steenland *et al.*, 1996; Muscat and Wynder, 1995; He *et al.*, 1994; Dobson *et al.*, 1991a; Kawachi *et al.*, 1997). In the CPS II study, any effect of workplace ETS exposure was small and was not statistically significant (Steenland *et al.*, 1996). However, in the Nurses' Health Study (Kawachi *et al.*, 1997), there was a strong effect of ETS at work and risk of CHD. A strong effect of ETS at work was also reported in a case-control study conducted in China (He *et al.*, 1994). This study in China differed from other case-control studies in that all cases and controls had full time jobs and thus had the opportunity to be exposed at work. Most of the other studies (Muscat and Wynder, 1995; Butler, 1988; Dobson *et al.*, 1991a) had limited ability to investigate the role of workplace ETS exposure since only small numbers of subjects had jobs outside the home.

A second concern is the lack of or inadequate control for confounding factors. Although information on the established risk factors for CHD were not available in all studies, including two large cohort studies (Hirayama, 1984; Helsing *et al.*, 1988), the recent large cohort studies conducted by Steenland *et al.* (1996) using the CPS II cohort and by Kawachi *et al.* (1997) using the Nurses' Health Study included a large number of dietary and non-dietary potential confounders in their analyses. A concern is that nonsmokers with smoking spouses may differ from nonsmokers with nonsmoking spouses in other lifestyle habits that are related to heart disease. There is, however, little evidence that this could have explained the observed findings. In the studies which presented data on other heart disease risk factors (blood pressure, cholesterol, body mass index) and dietary habits among nonsmokers stratified by the smoking status of their spouses (Garland *et al.*, 1985; Svendsen *et al.*, 1987; Humble *et al.* 1990; La Vecchia *et al.*, 1993), nonsmoking women married to nonsmokers and those married to smokers were generally similar in other risk factors for heart disease. More importantly, in the studies which presented relative risks adjusting for demographic factors only (i.e., age and sex), and relative risks adjusting for demographic factors and other CHD risk factors, the latter relative risks were not invariably lower after such adjustment (Garland *et al.*, 1985; Svendsen *et al.*, 1987; Butler, 1988; Humble *et al.*, 1990). In the Nurses' Health Study (Kawachi *et al.*, 1997), although there was some reduction in the relative risk with adjustment of various potential confounders, the risks remained elevated and were statistically significant.

A more fundamental question is whether the ETS association observed is biologically plausible (see Section 8.3) and whether the magnitude of the effect is consistent with the active smoking relationship with CHD. Although the majority of studies have found a significant positive association between active smoking and CHD in men and in women (U.S. DHHS, 1983), there have been some inconsistent findings (Kannel, 1976). The evidence most often cited as demonstrating no association between CHD and active smoking is the negative finding for uncomplicated angina pectoris in women reported in the Framingham study (Seltzer 1991a and 1991b; Skrabanek, 1992). This negative finding has been attributed to the low percentage of women who smoked in this population, and to the fact that even among women who smoked, most were light smokers, and thus the study did not have the power to detect a significant association (Kuller and Meilahn, 1991). A significant positive association between active

smoking and CHD in women has been observed repeatedly in more recent cohort studies and in numerous case-control studies (Table 8.3). The strongest evidence is from a large U.S. cohort study of nurses in which significant increased risks for nonfatal MI, angina, and fatal CHD were observed for smokers compared to nonsmokers, demonstrating an increasing trend in risk with increasing amounts of cigarettes smoked (Willett *et al.*, 1987) (Table 8.3). The relative risks for CHD in relation to light smoking reported in recent studies are considerably higher than the risk estimates reported in studies conducted in the 1950-1960. Specifically, in earlier cohort studies, relative risks of 1.2 to 1.6 were generally reported for men smoking 1-9 cigarettes/day compared to nonsmokers, as noted in a previous review (Wu-Williams and Samet, 1990). In more recent studies, relative risks of 2 to 3 were reported for women (Willett *et al.*, 1987; Palmer *et al.*, 1989) (Table 8.3) and men (Rosengren *et al.*, 1992) who were light smokers (1-4 or 5-14 cigarettes/day) compared to nonsmokers. The higher relative risks for CHD in more recent cohorts may be due to the earlier age of smoking initiation or deeper inhalation during smoking. The two to three fold risk between active smoking and CHD in contemporaneous studies suggest that the increased risk of about 30 percent for ETS exposure and CHD is believable. As described above, the Nurses' Health Study (Kawachi *et al*., 1997) allowed direct comparison of the risk of active smoking versus passive smoking relative to the same baseline group (that is, never-smoking women not exposed to ETS) and showed that the effect of ETS exposure at home and at work combined was approximately 75% of that of active smoking of 1-4 cigarettes per day.

Because there is some variation in the strength of the association between active smoking and various CHD endpoints, it is also important to distinguish between the different CHD outcomes in studies of ETS. In studies on active smoking and heart disease, the relative risks observed for MI and CHD deaths are usually stronger than the relative risks for angina (Willett *et al.*, 1987; Beard *et al.*, 1989) (Table 8.3). In studies of ETS and heart disease, some studies included fatal and nonfatal endpoints (Svendsen *et al.*, 1987; Hole *et al.*, 1989; Dobson *et al.*, 1991a; Kawachi *et al.*, 1997) while other studies included only fatal endpoints (Hirayama, 1984; Garland *et al.*, 1985; Helsing *et al.*, 1988; Humble *et al.*, 1990; Layard, 1995; LeVois and Layard, 1995; Steenland *et al.*, 1996) or nonfatal endpoints (Lee *et al.*, 1986; He *et al.*, 1989 and 1994; LaVecchia *et al.*, 1993; Muscat and Wynder, 1995). It is difficult to directly compare these results since most cohort studies provided information on fatal CHD whereas most of the case-control studies provided information on nonfatal CHD endpoints. Two studies allow direct comparison of the association between ETS exposure and risk of fatal and nonfatal endpoints. In one study (Hole *et al.*, 1989), results were presented separately for angina pectoris and for CHD deaths, and the effect of ETS was stronger for CHD deaths than for angina or other cardiovascular disease symptoms. In another study, the relative risks presented for fatal CHD events were higher than the relative risks for fatal and nonfatal endpoints combined, suggesting that the effect for nonfatal events was weaker and had diluted the overall association (Svendsen *et al.*, 1987).

There is some suggestion that the association between active smoking and CHD may be stronger in younger subjects than in older subjects (Bush and Comstock, 1983; Rosenberg *et al.*, 1985), although in some studies, the difference in relative risks by age was only apparent among the very heavy smokers (Willett *et al.*, 1987; Gramenzi *et al.*, 1989) (Table 8.4). Two studies presented findings on ETS and CHD by age group. In one study, there was an apparent effect in the younger age group (25-44 years) and in the older age group (65+) (Helsing *et al.*, 1988). In

another study (Steenland *et al.*, 1996), the association between risk of CHD mortality and exposure to spouses seemed to be more apparent for subjects aged < 65 years old. This suggests that age-specific effects, and cohort effects of ETS exposure on risk of heart disease should be monitored in future studies.

8.3 Other Supportive Evidence

It is important to identify the mechanisms whereby exposure to ETS increases the risk of CHD in nonsmokers, and to understand reasons for the relatively large effects of ETS on heart disease in nonsmokers compared to the magnitude of the effect of active smoking on heart disease. At least five interrelated processes have been proposed to contribute to the clinical manifestations of MI, including: atherosclerosis, thrombosis, coronary artery spasm, cardiac arrhythmia, and reduced capacity of the blood to deliver oxygen (U.S. DHHS, 1990). The evidence that active smoking influences these mechanisms is convincing (U.S. DHHS, 1990). Supportive evidence is accumulating that exposure to ETS may also increase the risk of some of these same interrelated processes. The effects of ETS on intermediate processes including internal and common carotid wall thickness, endothelial function, exercise tolerance, lipid profile, platelet function, and fibrinogen levels have been investigated and are reviewed below.

8.3.1 Internal and common carotid wall thickness

Hospital-based and population-based studies (Howard *et al.*, 1994; Tell *et al.*, 1994) have demonstrated that active smoking is associated with significantly greater internal and common carotid wall thickening. The relationship between ETS exposure and carotid wall thickening has been investigated in a large cross-sectional (Howard *et al.*, 1994) and a longitudinal study (Diez-Roux *et al.*, 1995). The cross-sectional study was conducted among participants in the Atherosclerosis Risk in Communities (ARIC) Study. At the baseline examination conducted in 1987 through 1989, carotid artery intimal-medial thickness (IMT) was measured using B-mode real-time ultrasound and exposure to active and passive smoking was assessed by questionnaires administered to about 15,800 adults aged 45 to 65 years. Sixty percent of the study subjects were either current or past smokers and the remainder were never smokers. Never smokers were considered exposed to ETS (n=3339) if they reported current exposure for 1 or more hours per week to ETS and as not exposed (n=1774) if they had no regular weekly exposure to ETS. Mean IMT (mm) was higher in nonsmokers exposed to ETS (0.711) than in nonsmokers not exposed to ETS (0.700), but the mean IMT values in both groups of nonsmokers were considerably lower than those in past smokers (0.772) or current smokers (0.775). These differences in IMT between ETS exposed and nonexposed nonsmokers were observed in each age, race, and gender group. After adjustment for age, race, and gender, a significant difference in IMT of 0.017 mm was estimated between ETS exposed and nonexposed nonsmokers. Further adjustments for other risk factors reduced the difference to 0.013 mm, which remained statistically significant (Table 8.8). The number of hours of ETS exposure was significantly associated with IMT in men but not in women in this study. Among nonsmoking men with ETS exposure (n=885), after adjustment for age and race, there was an increase of IMT of 0.00792 mm per 10 hours of weekly ETS exposure ($p<0.001$). In women with ETS exposure (n=2340), the increase of IMT was o.0011mm per 10 hours of weekly ETS exposure ($p=0.43$).

Results from a longitudinal study further support the association between ETS exposure and carotid artery IMT. In 1975, a population census which also asked about active smoking and household smoking was conducted in Washington County, MD, one of the study populations of the ARIC study (Howard *et al.*, 1994). Diez-Roux *et al.* (1995) linked the household smoke exposure data obtained in 1975 to carotid IMT measurements obtained 12-14 years later in the ARIC baseline visit to establish the temporality of the association of ETS exposure with carotid wall thickening. Information on ETS exposure in 1975 and 1987-1989, and carotid artery IMT was available on 2,073 subjects who had never smoked. In males and females combined, the adjusted mean IM wall thickness was 0.706, 0.731, 0.738, and 0.734, respectively, for subjects who had no ETS exposure, were exposed to ETS in 1975 only, were exposed to ETS in 1987-89 only, and were exposed to ETS in both study periods. This represented a 3.5 to 4.5% increase in intimal thickness in relation to ETS exposure. Mean wall thickness was found to be lowest among never smokers who had never been exposed to ETS, and ETS exposure in one or both time periods was associated with an increase in wall thickness ranging from 0.023 to 0.035 mm, after adjustment for other risk factors. All three groups exposed to ETS had consistently greater wall thickness than the no exposure group.

The significance of small increases in wall thickness in relation to ETS exposure is unclear. Analysis based on the entire ARIC cohort found that an increase of 0.16 in IMT was associated with a 24% increase in risk of coronary heart disease events in men and a 44% increase among women, over a 2.2 year follow-up period (Howard *et al.*, 1994). Among Finnish men, for each 0.1 mm increase in IM wall thickness the risk of MI increased by 11% (Salonen and Salonen, 1991 and 1993). The magnitude of the differences in carotid wall thickness associated with passive smoking is about one-fourth to one-fifth of that observed with active smoking and may contribute to the risk of future cardiovascular events. The magnitude and differences between active and passive smoking in terms of changes in carotid wall thickness are similar to the magnitudes of the differences in excess risk for these groups in terms of coronary heart disease endpoints.

8.3.2 Endothelium Function

Endothelial dysfunction is considered an important marker of early vascular damage. Celermajer *et al.* (1996) conducted a study which compared the endothelial function in the arteries of three groups of healthy teenagers and young adults: active smokers (n=26), lifelong nonsmokers who were exposed to ETS (passive smokers) (n=26), and lifelong nonsmokers who reported to have never been regularly exposed to ETS at home or at the workplace (n=25). Regular exposure to ETS was defined as self-reported exposure at home or at work or both for at least one hour per day for at least three years.

Vascular reactivity of the brachial artery was analyzed. The ultrasound method was used to measure brachial artery vascular responses to increased flow (an endothelium-dependent dilator stimulator) and to nitroglycerin (an endothelium-independent dilator). The diameter of the vessel was measured in every case by two independent observers who were blinded to the active and passive smoking status of the study subjects. Flow-mediated dilatation and nitroglycerin-induced dilatation were calculated by each observer, and the average results of the two observations were recorded.

Subjects in the three groups were similar in baseline characteristics including their age, systolic and diastolic blood pressure, total cholesterol, low-density and high-density lipoprotein cholesterol, vessel size at rest, and flow at rest. Not unexpectedly, the salivary cotinine levels (ng/ml) were significantly higher in the active smokers (170 ng/ml) compared to the passive smokers (3.7 ng/ml) and the nonsmokers (1.2 ng/ml).

The degree of reactive hyperemia produced by cuff inflation and release was similar in the three groups studied. In response to this increase in flow, arterial dilatation was 8.2 percent in the nonsmokers, 3.1 percent in the passive smokers, and 4.4 percent in the active smokers. Among the passive smokers, the percent flow-mediated dilatation was 4.1 in the subjects with light exposure to ETS, 3.1 in those with moderate exposure to ETS and 1.8 in those with heavy ETS exposure. There was no difference in the nitroglycerin-induced dilation in the three groups.

In this study passive smokers have significantly impaired arterial endothelial function. Impaired bioavailability of nitric oxide, the endothelium-derived relaxing factor, may be particularly important, since nitric oxide acts to inhibit platelet aggregation (Cooke and Tsao, 1994; Deanfield, 1996). Dilatation mediated by brachial-artery flow is endothelium-dependent and is mediated in part by the release of nitric oxide. The activity or production of endothelial nitric oxide may be impaired in young passive smokers as well as in active smokers. Although only superficial systemic arteries can be studied with this ultrasound-based method, endothelial dysfunction in the brachial artery appears to be well correlated with both coronary endothelial physiology and coronary atherosclerosis.

8.3.3 Exercise Tolerance

Of the many toxic agents in ETS, carbon monoxide is a main candidate to influence cardiovascular function, through several possible mechanisms. Carbon monoxide (CO) interferes with oxygen transport by binding to hemoglobin, forming carboxyhemoglobin, resulting in the displacement of oxygen and the lowering of the oxygen-carrying capacity of the blood. On a cellular level, carbon monoxide can interfere with intracellular oxidation processes and can increase platelet adhesiveness (Anthony, 1989; U.S. DHHS, 1983; U.S. DHHS, 1990). Thus, exposure to ETS, which is rich in carbon monoxide, may result in increased myocardial oxygen demand which in turn may outstrip the oxygen supply and produce ischemia. Carbon monoxide has also been reported to lower the ventricular fibrillation threshold and may accelerate atherogenesis by altering lipid metabolism or by altering vessel permeability to cholesterol. The COHb levels in nonsmokers exposed to ETS may be up to 1.5%. This level of COHb can be compared to levels of 4 to 6% among active smokers and 2 to 3% among certain occupational groups (e.g., blast furnace workers, traffic officers) (Schievelbein and Richter, 1984).

In four studies, the exercise performance of healthy subjects and subjects with a history of heart disease were evaluated under two conditions: in the absence of ETS exposure, and in the presence of ETS exposure. The conditions with ETS exposure simulate exposure levels typically encountered in public settings (Aronow, 1978; McMurray *et al.*, 1985; Leone *et al.*, 1991; Pimm *et al.*, 1978) (Table 8.5).

The study conducted by Aronow (1978) evaluated the exercise tolerance of 10 men who had classical stable exertional angina. This study tested the hypothesis that exposure to ETS may result in earlier onset of angina. The men were exposed to ETS in a well-ventilated room and in an unventilated room. Exposure to ETS resulted in elevation in resting heart rate, blood pressure, and carboxyhemoglobin levels under both room conditions, although the increase was more apparent when patients were exposed to ETS in an unventilated room. Corresponding with the increases in COHb levels, the duration of exercise until angina developed decreased 22% ($p<0.001$) after ETS exposure in the well-ventilated room and 35% ($p<0.001$) when the exposure occurred in the unventilated room. The carboxyhemoglobin level increased 42% ($p<0.001$) when exposure to ETS occurred in a well-ventilated room and 75% ($p<0.001$) when in an unventilated room.

Extending the findings of Aronow (1978), Leone *et al.* (1991) evaluated the acute effects of passive smoking on cardiac performance in 9 healthy subjects and 10 subjects with a history of MI. Healthy subjects were younger (mean age 30.5) than subjects with MI (mean age 53.8). Each subject underwent two exercise stress tests on a bicycle ergometer. The first test took place in an enclosed space not polluted by smoking whereas the second test occurred when the ambient atmosphere was polluted by 30-35 ppm CO.

The peak exercise power of healthy men was not altered by exposure to ETS. However, men with a history of MI experienced a 33% ($p<0.01$) reduction in peak exercise power (Table 8.5). The time to recovery of pre-exercise heart rate (in minutes) was significantly prolonged for both groups of men when they were exposed to ETS ($p<0.01$). Measured levels of expired carbon monoxide (ppm) pre-exercise and post-exercise were similar when there was no exposure to ETS, but were 4 times higher in healthy men and 9 times higher in men with previous MI when there was ETS exposure. Levels of plasma CO were also higher post-exercise than pre-exercise in the ETS exposed group, although a significant increase was observed only among men with a history of MI.

McMurray *et al.* (1985) evaluated the effects of ETS on submaximal and maximal exercise performance in 8 young healthy women (4 smokers, 4 nonsmokers) who were regular participants in an aerobics class. Subjects ran on a motor driven treadmill at submaximal and maximal exercise speeds when there was no ETS exposure and with ETS exposure by breathing air mixed with cigarette smoke (Table 8.5). At maximal exercise capacity, exposure to ETS reduced maximal oxygen uptake (11%, $p<0.05$) and the duration of exercise (9%, $p<0.05$). Increased values in the following parameters occurred: maximal respiratory exchange ratio (8%), maximal blood lactate (24%, $p<0.05$), ratings of perceived exertion (9%, $p<0.05$), and the ratio of ventilation to oxygen uptake (Ve/Vo_2 ratio, in liter/min) (10%, $p<0.05$). Similar adverse effects of ETS exposure were observed under submaximal exercise although statistically significant differences were observed for only some of the parameters measured (Table 8.5).

In a fourth study (Pimm *et al.*, 1978), the exercise responses of 20 healthy young men and women were compared after 7 minutes of exercise on an electronic bicycle ergometer when they were not exposed to ETS and when they were exposed to an environment with about 24 ppm of carbon monoxide produced by smoking 4 cigarettes. Heart rate, number of breaths per minute, ventilation rate (liter/min), and maximum oxygen uptake test (VO_2, liters/min) were measured as

an assessment of exercise response. For both men and women, carboxyhemoglobin levels increased significantly when exposed to ETS but there were few consistent changes in measures of lung volumes or in exercise responses. The lack of significant changes in exercise responses in these healthy subjects is in fact consistent with results in more recent studies. Compromised exercise performance was more easily demonstrated in subjects with a history of heart disease than in healthy subjects (Leone *et al.*, 1991). Moreover, the exercise test in this study is similar to the submaximal exercise challenge in the study of McMurray *et al.* (1985) in which fewer significant differences were observed compared to the maximal exercise challenge. Most of the parameters studied by McMurray *et al* (1985) were not measured by Pimm *et al.* (1978.

In two other studies (Allred *et al.*, 1989; Sheps *et al.*, 1990), exercise performance of subjects with a history of coronary artery disease was shown to be compromised when carbon monoxide was introduced into the environment, resulting in exacerbated ventricular arrhythmias (Sheps *et al.*, 1990) and myocardial ischemia (Allred *et al.*, 1989). These studies differed from previous studies (see Table 8.5) in that the amount of carbon monoxide introduced into the chambers was higher, ranging from 100 to 250 ppm, exceeding levels generally reported for public places such as restaurants and bars with tobacco smoke exposure. The carboxyhemoglobin levels in test subjects were 4 to 6% in one study (Sheps *et al.*, 1990) and 2 to 4% in another study (Allred *et al.*, 1989).

In summary, the collective evidence suggests that exposure to ETS containing levels of carbon monoxide that may be encountered in public settings with tobacco smoke exposure has deleterious effects on the heart by increasing the demands on the heart during exercise and reducing its capacity to respond. This imbalance increases the ischemic stress of exercise in patients with existing coronary artery disease and may precipitate symptoms. The data also suggest that even among healthy subjects, exposure to ETS may similarly impair exercise tolerance, although to a lesser extent.

8.3.4 Lipid profile

An altered serum lipid profile is an established risk factor for CHD. Determinants of the serum concentrations of the various lipids include diet, exercise, smoking, and genetic factors. A mechanism whereby smoking influences the risk of CHD is by changing the serum lipid fractions into a more atherogenic profile, i.e., higher levels of low-density lipoprotein cholesterol (LDL-C) and reduced levels of high-density lipoprotein cholesterol (HDL-C) (U.S. DHHS, 1990). The strongest and most consistent effect of smoking on lipid profile is to lower concentrations of high density lipoproteins (HDL). In different studies, HDL levels were 3 to 8% lower in male smokers compared to male nonsmokers and 11 to 13% lower in female smokers compared to female nonsmokers (Anthony, 1989). There is also the suggestion that smokers have higher levels of triglyceride and total cholesterol compared to nonsmokers, but the differences were generally small and the data are not consistent (Anthony, 1989). The effect of smoking on HDL cholesterol levels may be through the effect of nicotine on catecholamine levels (Anthony, 1989).

Two studies have examined the relationship between ETS exposure and lipid profiles in healthy adolescents (Table 8.6). The results from these studies suggest that ETS exposure may elevate plasma lipid levels and change lipoprotein distribution, resulting in an elevated ratio of total

cholesterol (C) to HDL-C (total C/HDL-C ratio). The total C/HDL-C ratio is used as a predictor of the risk of CHD since a high ratio generally means high levels of total C and low levels of HDL.

Moskowitz *et al.* (1990) studied the effects of ETS exposure on the cardiovascular and oxygen transport system of 216 preadolescent twins, 105 of whom had at least one parent who smoked and 111 had both nonsmoking parents. Blood samples were collected on almost all subjects and levels of thiocyanate and cotinine were used as measures of smoke exposure in the children. Levels of total cholesterol and subfractions were also assessed. Only data from a single twin randomly selected from each family were used for statistical analysis.

Children who were passively exposed to parents' smoking showed significantly higher levels of thiocyanate (7.1 vs 3.1 mg/L, $p<0.0001$), cotinine (1.5 ng/ml vs non-detectable levels), and 2-3 diphosphoglycerate (DPG) (2.09 vs 1.97 μm/ml, $p<0.001$) compared to children not exposed to parents' smoking. The level of DPG is used as a marker of the body's response to hypoxia, to meeting tissue oxygen demands. Corresponding to these increases, there were significant reductions in levels of HDL (6.3%, $p<0.05$) and total cholesterol (4.7%, $p<0.05$) among children passively exposed compared to those not exposed when age, weight, height, and gender were adjusted for in the analysis. There is internal consistency in the data such that within smoking families, significant positive correlations were observed between thiocyanate levels and total number of cigarettes parents smoked per day ($r=0.35$, $p<0.0001$), between thiocyanate and cotinine levels ($r=0.44$, $p<0.0001$), and between thiocyanate and DPG levels ($r=0.29$, $p<0.02$).

In another study, Feldman *et al.* (1991) compared the ratio of total C/HDL-C in children stratified by exposure to ETS. Included in this analysis were 391 adolescents (presumed to be nonsmokers), of whom 44% reported that one or both parents currently smoked, 22% reported exposure to smoking of friends/siblings only, and 34% reported no exposure. In the main analysis, total C/HDL-C ratio in adolescents whose plasma cotinine levels were ≥ 2.5 ng/mL ($n = 57$) (the level considered indicative of exposure) was compared to those with lower cotinine levels. Eighty-two percent of subjects with cotinine levels ≥ 2.5 ng/mL reported exposure to ETS. Plasma cotinine levels ≥ 2.5 ng/mL were associated with low HDL/C and a higher ratio of total C to HDL-C levels. The total C/HDL-C ratio was 8.9% ($p<0.003$) greater and the mean HDL-C level was 6.8% ($p <0.03$) lower in adolescents with higher plasma cotinine (≥2.5 ng/ml) concentration compared to those with lower cotinine levels. We calculated total C/HDL-C ratios of 3.92 and 3.51, respectively, for children with cotinine levels ≥2.5 ng/ml and < 2.5 ng/ml (based on Table 4.2 of Feldman *et al.*, 1991). The higher total C/HDL-C ratios among adolescents with higher cotinine levels were observed regardless of their source of ETS exposure. Information on dietary habits and socioeconomic status were not available in either the Feldman *et al.* (1991) or the Moskowitz *et al.* (1990) study, precluding adjustment for potential confounding effects on the observed association.

The change in lipid profiles among nonsmoking children exposed to ETS compared to nonsmoking children not exposed is compatible with the change observed when children who smoke are compared to nonsmoking children. In a meta-analysis which examined cigarette smoking associated changes in blood lipid and lipoprotein levels in 8 to 19 year olds, Craig *et al.*

(1990) reported that active smokers showed significantly lower serum levels of HDL-C (8.5%) compared to nonsmoking children in the same age range. The HDL-C levels were 9% lower in active smokers compared to nonsmokers (Craig *et al.,* 1990) and 6-7% lower in nonsmokers exposed to ETS compared to nonsmokers not exposed (Moskowitz *et al.,* 1990; Feldman *et al.,* 1991).

Information on lipid profiles in nonsmoking adults exposed to ETS and those not exposed is available in the case-control study of He *et al.* (1989). Similar to the results in children, nonsmoking adults who were exposed to ETS also showed lower levels of HDL-C. The average levels were 1.29 nmol/L in nonsmoking women not exposed, and 1.41 nmol/L in nonsmoking women exposed to spouses' smoking (8.5% reduction, $p<0.05$).

In summary, the findings by Moskowitz *et al.* (1990) and Feldman *et al.* (1991), which show the effects of exposure to ETS on lipid levels, provide support for another mechanism whereby risk of heart disease in those exposed to ETS may be increased. The reduction in HDL-C levels among passive smokers is about two-thirds of that reported for active smokers, providing a possible explanation for the relatively large effect of ETS on heart disease in nonsmokers compared to the effect of active smoking on heart disease.

8.3.5 Platelet Aggregation and Endothelial Damage

Platelets have an important role in the development and progression of atherosclerosis. Although studies on the effect of smoking on platelet function are not all consistent, most studies point to an effect of smoking on the behavior of platelets (U.S. DHHS, 1990; Anthony, 1989; Ozdemir *et al.*, 1992; Rangemark *et al.*, 1992; Chiang *et al.*, 1992). Specifically, some of the changes in platelets that have been demonstrated in smokers compared to nonsmokers include shorter platelet survival (Mustard, 1981), increased response to aggregation induced by various agents including adenosine diphosphate (ADP) or thrombin (Renaud *et al.*, 1984; Blache *et al.*, 1992; Rival *et al.*, 1987), elevated serum and urinary levels of thromboxane and its metabolites (Dotevall *et al.*, 1992; Rangemark *et al.*, 1992; Nowak *et al.*, 1987), decreased endothelial prostacyclin (PGI_2) synthesis (Madsen and Dyerberg, 1984) and decreased platelet sensitivity to PGI_2 (Burghuber *et al.*, 1982; 1986). An increase in levels of thrombaxone, a platelet aggregating agent and a vasoconstrictor, in conjunction with a reduction in the levels of PGI_2, an inhibitor of platelet aggregation and a vasodilator, in smokers suggest an imbalance in hemostatic function in favor of aggregation. The overall effect of smoking tends to increase the ease with which platelets aggregate and the ease with which platelet mediators are released (Anthony, 1989).

Of the various measures of platelet functions that have been investigated in active smokers (see above), platelet sensitivity to PGI_2 in smokers and nonsmokers exposed to ETS has been investigated (Sinzinger and Kefalides, 1982; Burghuber *et al.*, 1986).

In one study, platelet sensitivity to the anti-aggregatory prostaglandins before, during, and after ETS exposure in smokers and nonsmokers was measured (Sinzinger and Kefalides, 1982). The unit of measurement of platelet sensitivity is the ID_{50}, i.e., the amount of prostaglandins (PG) in ng/ml platelet rich plasma necessary to halve the aggregation induced by 1 μmol/1 ADP.

Exposure to ETS, simulating the concentrations encountered in nightclubs and restaurants (i.e., exposing nonsmokers to smokers who smoked 30 cigarettes) reduced platelet sensitivity to the anti-aggregatory PG. The reduction was marked and was statistically significant in nonsmokers but not in smokers. It is of note that the baseline values were significantly lower ($p<0.01$) in smokers compared to nonsmokers, and that platelet sensitivity returned to basal values more quickly in nonsmokers than smokers (Table 8.7).

In another study, Burghuber *et al.,* (1986) studied the response of platelets to exogenous PGI_2 in terms of the sensitivity index of PGI_2 in chronic smokers and nonsmokers; levels in groups were measured under two sets of conditions: prior to and after actively smoking two cigarettes, and prior to and after exposure to an ETS contaminated atmosphere, respectively. To enable us to compare the results reported by Sinzenger and Kefalides (1982) and by Burghuber *et al.* (1986), we converted the latter results to the same units of measurement as the former study. Specifically, we calculated the ID_{50} by taking the reciprocal of the sensitivity index. In smokers and nonsmokers, the sensitivity index before and after active smoking and before and after ETS exposure is estimated from the data presented in Figures 3 and 4 of Burghuber *et al.* (1986) (Table 8.7). Similar to the findings of Sinzinger and Kefalides (1982), platelet sensitivity to PGI_2 in Burghuber *et al.* (1986) was significantly reduced after active smoking and after exposure to ETS. As shown in the study by Sinzinger and Kefalides (1982), the baseline values were in fact significantly lower in active smokers than in nonsmokers. The levels in nonsmokers even after active smoking or ETS exposure only approached the baseline levels of smokers. This study also suggests that platelets of smokers are less sensitive to the anti-aggregatory action of exogenous PGI_2 compared to platelets of nonsmokers. Acute inhalation of tobacco smoke decreases platelet sensitivity to PGI_2 only in nonsmokers, whereas no further decrease could be demonstrated in smokers. Thus, chronic active smoking or passive smoke exposure can desensitize blood platelets to PGI_2. Such platelets may be more ready to aggregate and participate in plug formation, leading to arterial thrombosis.

In addition to the effects on platelet function, smoking has been shown to have a desquamating effect on human endothelium, manifested by an increase in the concentration of anuclear carcasses of endothelial cells in venous blood (Preroxsky and Hladovec, 1979).

In a series of studies, Davis and colleagues compared the endothelial cell counts and platelet aggregate ratios when different types of tobacco products were smoked (Davis *et al.*, 1985; Davis *et al.*, 1990) and when nonsmokers were exposed to ETS (Davis *et al.*, 1989) (Table 8.8). In brief, these studies showed that the number of endothelial cells (per 0.9 µl chamber) more than doubled after smoking tobacco cigarettes, increased by 20% after smoking non-tobacco cigarettes (made from wheat, cocoa, and citrus plants), and increased by 32% after ETS exposure compared to less than 5% increase under control conditions (i.e., no exposure to ETS). Platelet aggregate ratios decreased 19% ($p<0.0002$), 4% ($p=0.004$), and 10% ($p=0.002$) respectively, after smoking tobacco cigarettes, non-tobacco cigarettes, and after exposure to ETS. There was no change in platelet aggregate ratios under control conditions (Table 8.8).

Nicotine is a potential cause of the observed changes in endothelial cells and platelet aggregate ratios after smoking tobacco cigarettes, although other components of cigarette smoke may be important. The modest changes in endothelial cells and platelet aggregate ratios after exposure to

ETS may be related to the increase in nicotine and carboxyhemoglobin levels in the blood after exposure to ETS. The changes observed in relation to smoking non-tobacco cigarettes may be explained by the release of small amounts of catecholamines and modest elevation in nicotine levels even when non-tobacco cigarettes are smoked (Davis *et al.,* 1990). These studies demonstrate that brief exposure to ETS under naturally occurring environmental conditions has consistent acute effects on the endothelium and platelets similar to those of active smoking. The exact roles of carbon monoxide, nicotine, and other components of tobacco smoke as causes of observed effects on platelets and the endothelium remain unclear; however, both of the effects seen following exposure of nonsmokers to ETS, platelet activation and endothelial damage, are prominent among the mechanisms thought to be involved in atherosclerosis and arterial thrombosis. These observations suggest another mechanism whereby exposure to ETS may increase the risk of heart disease in nonsmokers.

8.3.6 Fibrinogen Levels

In numerous cross-sectional, case-control, and cohort studies (U.S. DHHS, 1990; Dobson *et al.,* 1991b, Meade *et al.*, 1993), fibrinogen levels have been found to be consistently elevated among smokers compared to nonsmokers. Fibrinogen levels are strong predictors of risk of CHD (Wilhelmsen *et al.,* 1984; Meade *et al.,* 1986; Kannel *et al.,* 1987) and are thought to act by promoting thrombogenesis (Meade *et al.*, 1987; Kannel *et al.,* 1987). Studies of exsmokers show that fibrinogen levels decreased with smoking cessation; the reduction is observed within one to two months of smoking cessation. There is some suggestion that fibrinogen levels in exsmokers approach those of never-smokers two to five years after smoking cessation (Meade *et al.,* 1987; Dobson *et al.*, 1991b).

In one case-control study (Dobson *et al.,* 1991a), levels of serum fibrinogen were determined among controls to test the hypothesis that fibrinogen concentrations would be higher in smokers than nonsmokers, and higher in nonsmokers exposed to ETS than in non-exposed nonsmokers. Fibrinogen concentrations were highest in current smokers, intermediate in exsmokers and lowest in nonsmokers, in men and women. Nonsmoking men exposed to ETS at home showed higher fibrinogen levels than nonsmoking men not exposed, but this was not observed in women. There was also no difference in levels of fibrinogen for nonsmokers exposed to ETS at work and those not exposed. (The mean fibrinogen concentrations and corresponding confidence intervals were presented in two figures in Dobson *et al.* (1991a) and the actual values could not be accurately determined from the figures).

8.3.7 Animal Studies

Some animal studies have demonstrated that short term exposure to ETS promotes the atherosclerotic process. Exposure to high levels of ETS significantly accelerated the development of atherosclerosis in the aorta and pulmonary artery in male New Zealand White rabbits maintained on a high cholesterol diet (Zhu *et al.,* 1993). In a follow-up study in test animals of the same sex and strain, exposure to ETS significantly accelerated the development of arterosclerosis; while these investigators found that β-blocker metoprolol decreased the development of arterosclerosis, it did not protect against the effects of ETS on atherosclerosis (Sun *et al.,* 1994), suggesting that the β-adrenergic receptor system is not involved in the

mechanism of ETS-induced atherosclerosis. In another study, the growth of existing atherosclerotic plaques was accelerated in young cockerels exposed to ETS compared to those not exposed (Penn and Snyder, 1993). Specifically, inhalation of ETS did not influence the number of plaques in this study, but caused a marked increase in plaque size as determined by plaque index measurements. The investigators hypothesized that ETS exposure did not induce formation of plaques but that it stimulated the proliferation of normally quiescent cells. In a subsequent study, ETS exposure levels were decreased by a factor of five and the effect was still seen (Penn *et al*., 1994). The investigators noted that ETS exposure at levels equal to or below those routinely encountered by people in smoke-filled environments were sufficient to promote arteriosclerotic plaque development. In Sprague-Dawley rats, ETS acutely increased LDL accumulation in perfused carotid arteries after a single exposure (Roberts *et al*., 1996).

Exposure to ETS increased myocardial infarct size in a rat (Sprague-Dawley) model of ischemia and reperfusion, and longer ETS exposure produced a larger effect on infarct size (Zhu *et al*. 1994). In an investigation of the mechanism by which ETS exposure causes this effect, L-arginine blocked the increase in myocardial infarct size produced by ETS in the same animal model, but had no effect on increased platelet aggregation resulting from ETS exposure (Zhu *et al*., 1996). Since L-arginine is a precursor to nitric oxide, the authors postulated that the protective effect on infarct size might be related to an inhibitory effect of nitric oxide on leukocyte- or free radical- induced injury.

8.4 Chapter Summary and Conclusions

In summary, the epidemiologic data, from prospective and case-control studies conducted in diverse populations, in males and in females, in western and eastern countries, are supportive of a causal association between ETS exposure from spouses and CHD mortality in nonsmokers. Prospective studies have the advantage that information on smoking status and exposure to ETS was obtained prior to diagnosis of heart disease, minimizing selective recall bias and misclassification bias associated with disease status. On the other hand, in some case-control studies, information on ETS exposure was more detailed and included exposure from spouses as well as from other sources. To the extent possible, estimates of risks were determined with adjustment for demographic factors, and often for other factors related to heart disease (e.g., blood pressure, serum cholesterol level, obesity index, dietary factors) which may potentially confound the ETS and heart disease association. Estimates of risks associated with ETS exposure were almost always strengthened when there was adjustment for other cofactors. An overall risk of about 30% is supported by the collective evidence and is within the range of risk estimates observed for active smoking and CHD in contemporaneous studies published since the 1970s and 1980s (e.g., RR = 2.4 for fatal CHD and nonfatal MI in women who smoked 1-4 cigarettes/day) (Willett *et al.*, 1987). The association between ETS and CHD is also consistent with the active smoking and CHD association in that the relationship is stronger for fatal CHD outcomes than for nonfatal outcomes and angina.

Supporting the epidemiologic evidence, there are data accumulating from clinical studies which suggest various mechanisms for a causal association between ETS and heart disease. In a number of studies in which nonsmokers were exposed to ETS, carotid wall thickening and compromise of endothelial function were similar but less extensive than that experienced by

active smokers. In nonsmokers, including well subjects and those with a history of heart disease, exercise performance is compromised when exercise tests occurred under conditions with ETS exposure. There are also data which show that nonsmokers exposed to ETS compared to those with no exposure show a lipid profile that is more atherogenic. In studies of adolescents as well as adults, the reduction of HDL-C levels in nonsmokers exposed to ETS was about two-thirds of that observed when active smokers were compared to nonsmokers. Of the different parameters of platelet function that may be affected by active smoking, platelet sensitivity to the anti-aggregatory effect of PGI has been investigated in nonsmokers. In nonsmokers exposed to ETS, the concentration of PGI_2 required to inhibit platelet aggregation increased 40-70 percent. There was also an increase in the number of desquamating endothelial cells in nonsmokers exposed to ETS. These data collectively show that deleterious effects seen following ETS exposure may account for both short-term and long-term effects of ETS exposure on the heart.

TABLE 8.1
COHORT STUDIES ON ETS EXPOSURE AND HEART DISEASE

Geographical Area (Reference)	Cohort - Years of Follow-up; # of Deaths Due to Heart Disease	Exposure to ETS	Results			Comments
			Person Years	CHD deaths	Relative Risks (95% CI)	
Loma Linda, California (Butler, 1988)	Spouse Pair Cohort • 9785 nonsmoking Seventh-Day Adventists • followed between 1976-1982 • 87 CHD deaths in nonsmoking women AHSMOG Cohort • 2345 males and 4122 females of whom 1489 males and 3488 never smoked •followed between 1976-1982 •70 females deaths and 76 male deaths from CHD in never smokers	Spouse Pair Cohort <u>Husbands smoking</u> Never Past Current AHSMOG Cohort <u>Females</u> Lived with a smoker 0 1-10 yrs 11 + yrs Worked with a smoker 0 1-10 yrs 11 + yrs <u>Males</u> Lived with a smoker 0 1-10 yrs 11 + yrs Worked with a smoker 0 1-10 yrs 11 + yrs	 43053 8092 2487 12826 3301 8215 13870 5802 4670 8725 1729 3126 7999 3160 2420	 60 16 4 33 9 28 44 13 13 62 3 10 53 13 9	 1.00 0.96 (0.6-1.7) 1.40 (0.5-3.8) 1.00 1.46 (0.7-3.1) 1.53 (0.9-2.5) 1.0 1.85 (1.0-3.4) 1.86 (1.0-3.5) 1.00 0.41 (0.1-1.3) 0.61 (0.3-1.2) 1.00 1.26 (0.7-2.3) 0.76 (0.4-1.6)	Spouse Pair Cohort • RRs adjusted age. AHSMOG Cohort •RRs adjusted for age

TABLE 8.1 (continued)
COHORT STUDIES ON ETS EXPOSURE AND HEART DISEASE

Geographical Area (Reference)	Cohort Description	Exposure to ETS	Results			Comments
			Population at Risk:	#Events (CHD)	Relative Risk (95% CI)	
Japan (Hirayama, 1984)	• 91,540 nonsmoking women. • study conducted in 1966-1981 • subjects followed for 16 years • 494 coronary heart disease (CHD) deaths	Husband's smoking habits: nonsmoker exsmoker or smoked 1-19 cig/day 20+ cig/day	 21895 44184 25461	 118 240 136	 1.0 1.0 (0.9-1.3) 1.3 (1.1-1.6)	• RRs adjusted for husband's age and occupation.
San Diego (Garland, *et al*., 1985)	• 695 currently married nonsmoking women. • study conducted in 1972-74 • subjects followed for 10 years • 19 CHD deaths	Husband's smoking habits: never smoker exsmoker current smoker	 203 395 97	 2 15 2	 1.0 3.0[a] 2.3	• RRs adjusted for age only. • The RR adjusted for age, systolic blood pressure, total plasma cholesterol, obesity, and years of marriage was 2.7 for husbands who were ex- or current smokers compared to husbands whod did not smoke.

[a] 95% confidence interval is not available.

TABLE 8.1 (Continued)
COHORT STUDIES ON ETS EXPOSURE AND HEART DISEASE

Geographical Area (Reference)	Cohort Description	Exposure to ETS	Results			Comments
			Population at Risk:	#Events (CHD)	Relative Risk (95% CI)	
18 Cities in the U.S. (Svendsen, 1987)	• 1245 never smoking married men • study conducted in 1973 • subjects followed for 7 years till 1982 • endpoints included CHD, fatal and nonfatal events	Wives smoking habits:				• RRs presented are adjusted for age, baseline blood pressure, cholesterol, weight, drinks/wk and education. • RRs on coworkers' smoking were adjusted for age and wives' smoking status.
			(CHD deaths)			
		never smoker	959	8	1.0	
		smoker	286	5	2.23 (0.7-6.9)	
			(Fatal and nonfatal CHD)			
		never smoker	959	48	1.0	
		smoker	286	21	1.61 (1.0-2.7)	
			(For CHD deaths)			
		coworkers smoked				
		No	na	na	1.0	
		Yes	na	na	2.6 (0.5-12.7)	
			(Fatal and nonfatal CHD)			
		coworkers smoked				
		No	na	na	1.0	
		Yes	na	na	1.4 (0.8-2.5)	

TABLE 8.1 (Continued)
COHORT STUDIES ON ETS EXPOSURE AND HEART DISEASE

Geographical Area (Reference)	Cohort Description	Exposure to ETS	Results			Comments
			Population at Risk:	#Events (CHD)	Relative Risk (95% CI)	
Washington County, Maryland (Helsing, 1988)	• 3,454 white men and 12,348 white women never smoked •study conducted in 1963 •subjects followed through mid-1975 • 370 CHD deaths in men and 988 CHD deaths in women.	<u>Household passive smoking score</u> Males: 0 1+ 1-5 6-12 Females: 0 1+ 1-5 6-12	 2434 1020 459 561 4259 8086 3412 4674	 248 122 56 66 437 551 252 299	 1.0 1.31 (1.1-1.6) 1.38 (1.1-1.8) 1.25 (1.0-1.6) 1.0 1.24 (1.1 1.4) 1.20 (1.0-1.4) 1.27 (1.1-1.5)	• RR adjusted for age, housing quality, schooling, marital status.

TABLE 8.1 (Continued)
COHORT STUDIES ON ETS EXPOSURE AND HEART DISEASE

Geographical Area (Reference)	Cohort - Years of Follow-up; # of Deaths Due to Heart Disease	Exposure to ETS	Results			Comments
			Population at risk:	# Events	Relative Risks (95% CI)	
Western Scotland (Hole, 1989)	• 15,399 residents aged 45-64, completed self-administered questionnaire between 1972-1976 • followed for an average of 11.5 years • 917 never smoker 1538 passive smokers • endpoints: heart disease symptoms including angina, and ischemic heart disease (IHD) death	Males and females	<u>Angina</u>			• RRs adjusted for age, sex, social class, diastolic blood pressure, serum cholesterol body mass index.
		never smoker	917	43	1.00	
		passive smoker	1538	74	1.11 (0.7, 1.7)	
		Males and females	<u>IHD deaths</u>			
		never smoker	917	30	1.00	
		passive smoker	1538	54	2.01 (1.2, 3.4)	

TABLE 8.1 (Continued)
COHORT STUDIES ON ETS EXPOSURE AND HEART DISEASE

Geographical Area (Reference)	Cohort - Years of Follow-up; # of Deaths Due to Heart Disease	Exposure to ETS	Results			Comments
			Population at risk	# Events (CVD deaths)	Relative Risks (95% CI)	
Evans County, Georgia (Humble, 1990)	• 1127 women, 943 were nonsmokers, 513 were married to never or current smokers •study conducted in 1960-61 • subjects followed for 20 years • endpoints included cardiovascular disease death (CVD), smoking related CVD, and all causes	Husband smoker vs. nonsmoker All subjects Blacks Whites (by social class) high low	 513 185 161 167	 76 na na na	 1.59 (1.0, 2.6) 1.78 (0.9, 3.7) 1.97 (0.7, 5.3) 0.79 (0.3, 2.0)	• Women whose husbands were exsmokers were excluded. • Baseline comparison group was women whose husbands never smoked. • RRs adjusted for age, blood pressure, cholesterol, and body mass index.

TABLE 8.1 (continued)
COHORT STUDIES ON ETS EXPOSURE AND HEART DISEASE

Geographical Area (Reference)	Cohort Description	Exposure to ETS	Males OR	Males 95% CI	Females OR	Females 95% CI	Comments
United States (Le Vois and Layard, 1995)	CPS-I •Total of 88,458 male and 247,412 female never smokers •CHD deaths: 7768 in males 7133 in females	Exposed to: Any smoking spouse Former smoker #cigarettes/day 1-19 20-39 40+	 0.97 0.95 0.99 0.98 0.96	 0.90-1.05 0.83-1.09 0.89-1.09 0.85-1.18 0.78-1.15	 1.08? 0.99 1.04 1.06 0.96	 0.98-1.08 0.93-1.06 0.97-1.12 0.98-1.16 0.78-1.15	•ORs presented were adjusted for age and race. Further adjustment for weight, exercise, education, dietary factors, history of hypertension and diabetes did not have any appreciable effect on risks. These ORs were not presented.
	CPS-II •108,772 male and 226,067 female never smokers; smoking status of spouses was known •CHD deaths: 1966 in males 1099 in females	Exposed to: Any smoking spouse Former smoker #cigarettes/day 1-19 20-39 40+	 0.97 0.81 1.36 1.28 1.13	 0.87-1.08 0.70-0.98 1.10-1.68 1.00-1.58 0.81-2.11	 1.00 0.99 1.14 0.98 1.27	 0.88-1.14 0.86-1.13 0.86-1.51 0.75-1.29 0.80-2.01	•Follow-up period during which these CHD deaths were observed was not described. •OR's were adjusted for age and race. ---------- •These analyses utilize the same datasets analyzed by Steenland et al. (1996) (see next page).

TABLE 8.1 (continued)
COHORT STUDIES ON ETS EXPOSURE AND HEART DISEASE

Geographical Area (Reference)	Cohort Description	Exposure to ETS	Males OR	Males 95% CI	Females OR	Females 95% CI	Comments
United States (Steenland et al., 1996)	Analysis 1 •Spousal cohort of 101,227 male and 208,372 female never smokers •CHD deaths: 2494 men 1325 women	Exposed to: Current smoker cigarettes/day <20 20 21-39 40+ Former smoker	1.22 1.33 1.17 1.09* 0.96	1.07-1.40 1.09-1.61 0.92-1.48 0.77-1.63 0.83-1.11	1.10 1.15 1.07 0.99 1.04 1.00	0.96-1.27 0.90-1.45 0.90-1.28 0.87-1.47 0.88-1.13 0.88-1.13	•These ORs were adjusted for age, self-reported history of heart disease, hypertension, diabetes, arthritis, body mass index, educational level, aspirin use, diuretic use, liquor consumption (in men), wine intake (in women), employment status, exercise, and estrogen use (in women).
	Analysis 2 •Spousal subcohort with single marriage and data on amount and duration of exposure to smoking during marriage •58,530 male and 99,821 female never smokers •CHD deaths: 1299 men 572 women	Exposed to: Current smoker Former smoker Years exposed to cigarette smoke 1-12 13-21 22-29 30+	1.48 0.97 1.14 1.13 1.14 1.25	1.21-1.80 0.79-1.20 0.80-1.63 0.80-1.69 0.84-1.56 1.01-1.53	1.18 1.08 0.84 0.99 1.20 1.20	0.91-1.46 0.90-1.29 0.59-1.20 0.73-1.39 0.91-1.59 0.96-1.46	--- •These analyses utilize the same datasets analyzed by LeVois and Layard (1995) (see preceding page).

* For those whose spouses smoke >21 cigarettes per day

TABLE 8.1 (continued)
COHORT STUDIES ON ETS EXPOSURE AND HEART DISEASE

Geographical Area (Reference)	Cohort Description	Exposure to ETS	Males OR	Males 95% CI	Females OR	Females 95% CI	Comments
United States (Steenland et al., 1996)	Analysis 3 •Subjects concordant for both self-reported current exposure to cigarettes and exposure based on spouse report •54,668 male and 80,549 female never smokers[?] •CHD deaths: 1180 men 426 women Analysis 4 •Restricted to those currently employed •76,710 male and 75,237 female never smokers •CHD deaths: 1751 men 768 women	Exposed currently Self-report: 1-2 hours/day 3-4 hours/day >4 hours/day Smoking reported by spouse: cigarettes/day <20 20 21-39 40+ Exposed at home Exposed at work Exposed elsewhere	1.23 1.23 1.35 1.13 1.37 1.15 1.12* 1.15 1.03 1.03	1.03-1.47 0.81-1.07 0.95-1.90 0.84-1.61 1.04-1.79 0.86-1.53 0.77-1.83 1.01-1.32 0.89-1.19 0.93-1.13	1.19 0.70 1.21 1.28 1.22 1.14 1.02 1.28 1.07 1.06 0.91	0.97-1.45 0.45-1.10 0.85-1.74 1.10-1.62 0.88-1.72 0.83-1.67 0.66-1.60 0.81-2.01 0.96-1.17 0.84-1.34 0.83-1.00	In analysis 4, the number of subjects in the cohort and the number of CHD deaths applied to the analysis for exposure at work. The numbers varied somewhat for the analyses on exposure at home and elsewhere.

* For those whose spouses smoke >21 cigarettes per day

TABLE 8.1 (continued)
COHORT STUDIES ON ETS EXPOSURE AND HEART DISEASE

Geographical Area (Reference)	Cohort Description	Exposure to ETS	Females OR 95% CI	Comments
United States Nurses' Health Study (Kawachi et al., 1997)	-121,700 nurses aged 30-55 years enrolled in 1976. -Questions on ETS exposure asked in a follow-up questionnaire in 1982 -32,046 women were never smokers; -follow-up between 1982-June 1, 1992 -152 incident CHD (127 nonfatal MI, 25 fatal CHD)	Exposure to ETS at home or at work never any occasional regular never any occasional regular never any occasional regular By years of living with smoker in adult life <1 1-9 10-19 20-29 30+	Total CHD 1.00 1.71 (1.03-2.84) 1.58 (0.93-2.68) 1.81 (1.11-3.28) Nonfatal MI 1.00 1.73 (0.99-3.03) 1.64 (0.92-2.93) 1.86 (1.04-3.42) Fatal CHD 1.00 1.87 (0.56-8.20) 1.50 (0.42-5.36) 2.55 (0.71-9.12) Total CHD 1.0 1.19 (0.75-1.90) 1.54 (0.99-2.40) 1.11 (0.89-1.77) 1.50 (0.97-2.32)	All ORs were adjusted for alcohol use, body mass index, history of hypertension, diabetes, hypercholesterolemia, menopausal status, use of hormones, physical activity, intake of Vitamin E and fat, use of aspirin and family history.

TABLE 8.2
CASE CONTROL STUDIES ON ETS EXPOSURE AND HEART DISEASE

Geographical Area (Reference)	Subjects (cases, controls) control type	Exposure to ETS	Cases/Controls	OR (95% CI)	Comments
United Kingdom (Lee, 1986)	- 507 males and females with IHD - hospital controls - a subset of cases and controls responded to questions on passive smoking	Nonsmoking men exposed to spouse No Yes Nonsmoking women exposed to spouse No Yes Nonsmoking men exposed to combined sources: score 0-1 2-4 5-12 Nonsmoking women exposed to combined sources: score 0-1 2-4 5-12	 26/93 15/40 22/89 55/229 15/27 12/55 3/15 23/75 9/61 4/21	 1.00 1.24 (0.6-2.8) 1.00 0.93 (0.6-1.7) 1.0 0.43(0.2-0.9) 0.43(0.1-1.4) 1.0 0.59 (0.2-1.1) 0.81 (0.2-2.0)	• Reason for varying sample sizes in analysis was not provided. • Combined index of exposure at home, work, during travel and leisure. A score of 0 to 3 is assigned separately to exposure at home, work, during travel, and leisure, for a maximum score of 12. Scores of 0 = not all; 1= little; 2 = average; 3 = a lot. • The confidence intervals were calculated based on the distribution of cases and controls presented in references.

TABLE 8.2 (Continued)
CASE CONTROL STUDIES ON ETS EXPOSURE AND HEART DISEASE

Geographical Area (Reference)	Subjects (cases, controls) control type	Exposure to ETS	Cases/Controls	OR (95% CI)	Comments
Newsouth Wales, Australia (Dobson, 1991)	- Subjects with myocardial infarction (MI) or coronary death, age 35-69, between July 1988-October 1989 - Controls selected from a community based risk-factor survey - Cases interviewed by nurses while in hospital, controls completed self-administered questionnaire	<u>Nonsmoking men</u> Not exposed at home Exposed at home Not exposed at work Exposed at work <u>Nonsmoking women</u> Not exposed at home Exposed at home Not exposed at work Exposed at work	 161/259 22/34 48/126 27/79 117/433 43/99 5/73 12/124	 1.00 0.97 (0.50, 1.86) 1.00 0.95 (0.51, 1.78) 1.00 2.46 (1.47, 4.13) 1.00 0.66 (0.17, 2.62)	• ORs adjusted for age, and history of MI • Only subset with information on exposure at work. • Data on passive smoke at work available on only a subset, reasons for missing data not explained.
People's Republic of China (He et al., 1989)	- 34 women CHD (12 MI, 22 diagnosed by coronary arteriography) - 68 controls (34 population, 34 hospital control)	<u>Nonsmoking women</u> Husband smoked Yes No	 9/38 16/25	 1.0 3.0 (1.3-7.2)	• The OR was adjusted for personal and family history of hypertension, family history of CHD, drinking, physical exercise and history of hyperlipidemia.

TABLE 8.2 (Continued)
CASE CONTROL STUDIES ON ETS EXPOSURE AND HEART DISEASE

Geographical Area (Reference)	Subjects (cases, controls) control type	Exposure to ETS	Cases/Controls	OR (95% CI)	Comments
Italy (La Vecchia et al., 1993)	- Acute MI patients 113 cases (44 females, 69 males) - Controls admitted to same hospitals for acute conditions not related to CHD	Spousal smoking habits	Males case/con / Females case/con		OR obtained from multiple regression; adjusted for sex, age, education, coffee intake, body mass index, serum cholesterol, hypertension, diabetes and family history of MI.
		never smoker	55/140 / 11/17	1.0	
		former smoker	2/4 / 15/19	0.91 (0.4-2.3)	
		current smoker	7/17 / 17/20	1.21 (0.6-2.5)	
		<15 cigarettes/d	5/11 / 6/8	1.13 (0.5-2.8)	
		15+ cigarettes/d	2/6 / 11/12	1.30 (0.5-3.4)	
People's Republic of China (He et al., 1994)	- Non-fatal CHD female cases in lifelong nonsmokers; identified from the 3 large teaching hospitals in Xian between 1989 and 1992; - Controls were from three sources and were combined in all analyses because they did not display significant differences by various characteristics	Passive smoking from			Crude ORs are shown.
		husband / work	cases / controls		
		no / no	11 / 50	1.0	
		yes / no	15 / 33	2.07 (0.8-5.6)	
		no / yes	10 / 18	2.42 (0.8-7.8)	
		yes / yes	23 / 25	4.18 (1.6-10.9)	
		Passive smoking at work			OR is adjusted for age, history of hypertension, personality type, total cholesterol, and passive smoking from husband.
		Number of smokers	cases / controls		
		0	26 / 83	1.00	
		1-2	16 / 36	1.16 (0.5-2.8)	
		3	12 / 6	5.06 (1.4-18.0)	
		4+	5 / 1	4.11 (0.4-43.7)	
		Test for trend			

TABLE 8.2 (Continued)
CASE CONTROL STUDIES ON ETS EXPOSURE AND HEART DISEASE

Geographical Area (Reference)	Subjects (cases, controls) control type	Exposure to ETS	Cases/Controls	OR (95% CI)	Comments
United States (Muscat and Wynder, 1995)	- Subjects with MI identified in four hospitals in the US between 1980-1990; hospital controls were used. - Cases and controls interviewed while in the hospital.	Adult exposure None 1-20 years 21-30 >30 None 1-20 years 21-30 >30	 <u>Males</u> 38/68 12/15 5/8 13/17 <u>Females</u> 13/20 12/8 5/9 16/13	 1.0 1.7 (0.7-4.5) 1.5 (0.4-5.2) 1.1 (0.4-2.8) 1.0 2.0 (0.5-8.1) 0.9 (0.2-4.4) 1.7 (0.5-5.9)	OR was adjusted for age, education and hypertension.
United States (Layard, 1995)	- Cases and controls were from National Mortality Follow-back Survey conducted in 1986. Next-of kin completed a self-administered questionnaire	<u>Spousal smoking</u> cigarettes/day none 1-<15 15-34 35+ cigarettes/day none 1-<15 15-34 35+	 <u>Males</u> 378/783 38/107 45/92 6/12 <u>Females</u> 459/969 139/336 224/405 52/111	 1.0 0.8 (0.5-1.1) 1.1 (0.7-1.6) 0.9 (0.9-2.6) 1.0 0.9 (0.7-1.1) 1.2 (0.9-1.4) 1.1 (0.7-1.5)	Causes of death of controls were not specified. ORs were adjusted for age and race; cases were significantly older than controls.

TABLE 8.2 (Continued)
CASE CONTROL STUDIES ON ETS EXPOSURE AND HEART DISEASE

Geographical Area (Reference)	Subjects (cases, controls) control type	Exposure to ETS	Cases/Controls	OR (95% CI)	Comments
New Zealand (Jackson, unpublished)	- Cases included acute MI patients and fatal CHD patients - Self-respondent population controls and next-of-kin of controls were compared to directly interviewed cases and next-of-kin of fatal CHD patients	Questions on ETS were added to an ongoing case-control study conducted in New Zealand.	Males: 28 acute MI cases compared to 123 controls; 21 fatal CHD cases compared to 61 controls Females: 11 acute MI cases compared to 112 controls; 9 fatal CHD cases compared to 62 controls	Acute MI: M 1.0 (0.3-4.3) F 2.7 (0.6-13.6) Fatal CHD: M 1.1 (0.2-4.5) F 5.8 (1.3-48.0)	ORs were adjusted for age and social class. The baseline comparison had no ETS exposure at home.

Abbreviations: MI = myocardial infarction; CHD = coronary heart disease

TABLE 8.3
RISKS OF HEART DISEASE AND ACTIVE SMOKING IN WOMEN

Cohort Study	Smoking Status	Person-Years	Fatal CHD # Event	RR	Nonfatal MI #Event	RR	Fatal CHD & Nonfatal MI #Event	RR	Angina # Event	RR	Comments
Willett, 1987	Nonsmoker	302,375	15	1.0	48	1.0	63	1.0	31	1.0	•U.S. cohort study of 119,404 nurses, aged 30-55, followed between 1976 to 1982.
	Exsmoker	174,237	11	1.2	44	1.5	55	1.5	30	1.6	
	Current (cig/day)										
	1-14	61,400	5	1.9	21	2.5	26	2.3	11	1.8	
	1-4	15,765	NA	NA	NA	NA	7	2.4	NA	NA	
	5-14	45,635	NA	NA	NA	NA	19	2.1	NA	NA	
	15-24	95,430	17	4.3	65	4.7	82	4.7	19	1.5	
	25+	63,359	17	5.4	64	6.3	81	6.1	17	2.3	

Case-control Studies	Smoking Status	CA/CO	RR	CA/CO	RR	Comments
Beard, 1989	Smoker		For CHD		For Angina	•CHD includes MI and sudden unexpected deaths.
	Yes	17/70	1.0	44/117	1.0	
	No	69/80	5.11*	84/115	2.77*	
						•Subjects aged 40-59.
Palmer, 1989	Active Smoking		For MI			•Multi-centered hospital -based cases and controls.
	Nonsmoker	191/940	1.0			
	Exsmoker	149/550	1.4 (1.0-1.8)			
	Current (cig/day)					•Cases between ages 25-64.
	1-4	11/36	2.4 (1.1-5.1)			
	5-14	54/140	2.5 (1.7-3.6)			
	15-24	213/412	3.0 (2.3-3.8)			
	25-34	110/136	5.1 (3.6-7.1)			
	35-44	120/129	4.9 (3.5-6.8)			
	≥45	58/21	22 (12-39)			
	any tobacco	570/885	3.7 (3.0-4.7)			

TABLE 8.3 (Continued)
RISKS OF HEART DISEASE AND ACTIVE SMOKING IN WOMEN

Case-control Studies	Smoking Status	CA/CO	RR for CHD	Comments
Gramenzi, 1989	Active Smoking		For MI	•Hospital-based study in Northern Italy, subjects aged 22-69.
	Nonsmoker	90/346	1.0	
	Exsmoker	10/16	1.5 (0.6-3.6)	
	Current (cig/day)			
	1-14	57/91	2.3 (1.4-3.7)	
	15-24	65/48	5.9 (3.2-9.3)	
	25+	40/18	11.0 (5.1-23.7)	
Rosenberg, 1985	Active Smoking		For MI	•Multi-centered US hospital-based study. •Subjects aged 25-49.
	Nonsmoker	73/571	1.0	
	Exsmoker	35/267	1.0 (0.7-1.6)	
	Current (cig/day)			
	1-14	40/211	1.4 (0.9-2.1)	
	15-24	139/449	2.4 (1.8-3.3)	
	25-34	96/152	5.0 (3.6-6.9)	
	35+	171/190	7.0 (5.2-9.4)	

NA - not available

TABLE 8.4
RISKS OF HEART DISEASE AND ACTIVE SMOKING IN WOMEN BY AGE

Case-control Studies	Smoke	# Event	RR	# Event	RR	# Event	RR	Comments
Willett, 1987	Active Smoking	Age 30-39		Age 40-49		Age 50-59		• Outcome: Fatal CHD and Nonfatal MI.
	Nonsmoker	5	1.0	20	1.0	38	1.0	
	Current (cig/day)							
	1-14	0	-	7	1.6 (1.1-2.4)	19	2.4 (1.5-3.9)	
	15-24	6	4.3 (1.3-13.7)	24	3.6 (2.4-5.5)	52	4.1 (2.9-5.9)	
	25+	3	3.5 (0.8-14.5)	33	7.0 (4.8-10.5)	45	5.3 (3.7-7.6)	
Bush and Comstock, 1983	Active Smoking	Age 25-44		Age 45-64		Age 65-74		• Outcome: Total arteriosclerotic heart disease deaths.
	Nonsmoker	12	1.0	219	1.0	355	1.0	
	Exsmoker	4	1.8	18	0.7	13	0.8	
	Current (cig/day)							• RRs adjusted for marital status, education, housing index, and frequency of church attendance.
	1-9	4	1.5	38	1.1	20	1.0	
	10-20	10	3.7	73	1.4	17	0.8	
	21+	8	2.4	36	2.2	1	0.1	•No information on other risk factors for heart disease.
	Active Smoking	Age 25-44		Age 45-64		Age 65-74		• Outcome: Arteriosclerotic heart disease, sudden.
	Nonsmoker	5	1.0	116	1.0	171	1.0	
	Exsmoker	4	4.6	11	0.9	10	1.2	
	Current (cig/day)							
	1-9	1	1.1	24	1.3	11	1.1	
	10-20	8	4.1	51	1.9	10	0.3	
	21+	6	7.5	24	2.8	1	0.4	

TABLE 8.4 (Continued)
RISKS OF HEART DISEASE AND ACTIVE SMOKING IN WOMEN BY AGE

Case-control Studies	Smoke	CA/CO	RR	CA/CO	RR	CA/CO	RR	Comments
Gramenzi, 1989	Active Smoking		Age <50		Age >50			• Outcome included acute myocardial infarction.
	Nonsmoker	na	1.0	na	1.0			
	Exsmoker	na	2.2	na	1.0			
	Current (cig/day)							• RRs adjusted for age, education, alcohol and coffee intake, diabetes, hypertension, hyperlipidaemia, body mass index, and use of oral contraceptives.
	<15	na	2.1	na	2.7			
	15-24	na	4.6	na	7.3			
	≥25	na	7.7	na	na			
Rosenberg *et al.*, 1985	Active smoking		Age 25-39		Age 40-44		Age 45-49	• Outcome included myocardial infarction.
	Nonsmoker	10/117	1.0	18/156	1.0	45/298	1.0	
	Exsmoker	5/48	1.2	4/86	0.4	26/133	1.3	• Unadjusted RRs.
	Current (cig/day)							
	1-14	4/47	1.0	8/56	1.2	28/108	1.7	
	15-24	25/101	2.9	40/154	2.3	74/194	2.5	
	25-34	23/27	10	28/56	4.3	45/69	4.3	
	≥35+	41/37	13	58/61	8.2	72/92	5.2	

TABLE 8.5
EFFECT OF EXPOSURE TO ETS ON EXERCISE TOLERANCE

Study	Study Subjects/Test	Parameter				
Aronow (1978)	•10 men with stable angina •exposed to 3 smokers who each smoked cigarettes over 2 hours •subjects exercised on bicycle ergometer until onset of angina		In Well-Ventilated Room Exposure to ETS		In Unventilated Room Exposure to ETS	
			No	Yes	No	Yes
		Duration of exercise in seconds (SD)	232.3 ± 68.4	181.1 ± 52.4[a]	233.7 ± 64.8	145.8 ± 36.9[a]
		Plasma Carboxyhemoglobin (%)	1.25 ± 0.20	1.77 ± 0.16[a]	1.30 ± 0.18	2.28 ± 0.15[a]
Leone (1991)	•19 nonsmoking males, 9 healthy and 10 with history of MI •exposed in an enclosed space with 30-35 ppm CO (with combustion of 15-20 cigarettes within 30 minutes) •subjects underwent exercise stress test on a bicycle ergometer twice		Healthy Subjects, Exposed to ETS		MI Patients Exposed to ETS	
			No	Yes	No	Yes
		Peak exercise (in seconds ± SD)	220 ± 30	220 ± 30	120 ± 20	80 ± 25[b]
		Time to recovery (μ min ± SD)	8.50 ± 4	19 ± 4[b]	12.3 ± 2	21 ± 2.5[b]
		Expired CO (ppm)				
		pre-exercise	2.3 ± 2	2.3 ± 2.01	1.2 ± 0.8	0.6 ± 0.2[c]
		post-exercise	2.1 ± 1.9	8.5 ± 1.6[d]	1.3 ± 0.6	5.2 ± 1.2[d]
		Plasma CO (%)				
		pre-exercise	1.2 ± 0.4	1.4 ± 0.2	1.2 ± 0.1	1.2 ± 0.16
		post-exercise	1.2 ± 0.4	1.7 ± 0.4	1.2 ± 0.3	2.3 ± 0.4[d]

[a] $p < 0.001$= Comparing exposed to ETS to not exposed under different ventilation conditions
[b] $p < 0.01$ = Comparing exposed to ETS to not exposed
[c] $p < 0.05$ = Comparing exposed to ETS to not exposed
[d] $p < 0.01$ = Comparing post-exercise to pre-exercise level among subjects exposed to ETS

TABLE 8.5 (Continued)
EFFECT OF EXPOSURE TO ETS ON EXERCISE TOLERANCE

Study	Study Subjects/Test		Results			
McMurray (1985)	•8 normal women, 4 smokers and 4 non-smokers exposed to pure air and air contaminated with ETS •subjects completed an exercise trial which included running 20 min at about 70% $VO_{2max.}$ • increase treadmill grade by 2-1/2% every 2 min until subject could not continue with exercise		Submaximal Exercise Exposure to ETS		Maximal Exercise Exposure to ETS	
			No	Yes	No	Yes
		Max 0_2 uptake (l/min)	1.82	1.85	2.39	2.13[a]
		Duration of exercise (minutes)	--	--	25.8	23.6[a]
		Maximal R value	0.86	0.91	0.93	1.01
		Lactate(mM)	--	--	5.5	6.8[a]
		Ratings of perceived exertion (units)	11.8	13.8[a]	16.5	17.4[a]
		Ve/$V0_2$ (l air/l 0_2)	27.5	28.4	30.5	33.5[a]
		Heart rate (beats/min)	173	178[a]	194	194

[a] $p < 0.05$, comparing exposed to ETS to not exposed under submaximal or maximal exercise.

TABLE 8.5 (Continued)
EFFECT OF EXPOSURE TO ETS ON EXERCISE TOLERANCE

Study	Study Subjects/Test		Results			
Pimm (1978)	•20 health men and women, ages 18-30 •exposed for 2 hours on alternate days to room air or air contaminated with tobacco smoke (about 24 ppm of CO) •subjects performed a 7-minute exercise test on an electronic bicycle ergometer (submaximum bicycle test)		Females (n = 10) Exposure to ETS[a]		Males (n = 10) Exposure to ETS	
			No	Yes	No	Yes
		Ventilation (l/min)	48.1	48.3	75.3	75.9[b]
		Number of breaths per minute	31.5	30.7	28.3	29.3
		Heart rate (beat/min)	164.1	168.7[b]	158.3	159.8
		VO_2 (l/min)	1.51	1.48	2.47	2.65[c]

[a] Values measured at 7 minutes of submaximum bicycle test.
[b] $p<0.01$ by paired to test.
[c] $p<0.05$ by paired to test.

TABLE 8.6
EFFECT OF EXPOSURE TO ETS ON LIPID PROFILE IN CHILDREN

Study	Study Subjects	Results							
Moskowitz (1990)	111 adolescents with both nonsmoking parents	Exposure to ETS	Thiocyanate (mg/L)	Cotinine (ng/ml)	Cholesterol (mg %)	LDL (mg %)	HDL (mg %)	HDL_2 (mg %)	HDL_3 (mg %)	2-3 DPG (µm/ml)
	105 adolescents with at least one smoking parent	No	3.1±5.0	ND[a]	172.2	86.1	49.1	13.5	35.6	1.97
		Yes	7.1±4.3	1.5±3.1	164.1*	81.3	46.0*	12.5	33.5*	2.09**
Feldman (1991)	•274 boys, 117 girls •34% no exposure; 15% mother smoked only; 17% father smoked only; 12% both parents smoked; 22% friends/siblings smoked.	Total Cholesterol/HDL-C Ratios (±SD) by Serum Cotinine Level								
				<2.5 ng/ml (n=347)[c]			≥ 2.5 ng/ml (n=44)[c]			
				3.51[c]			3.92			
		Exposure to ETS								
		None		3.47 (± 0.87)			3.77 (± 0.76)			
		Friend/sib only			3.55 (± 0.90)			3.70 (±1.13)		
		Mother, not father		3.34 ± 0.55)			4.06 (±1.00)			
		Father, not mother		3.64 (± 0.78)			4.22 (±1.04)			
		Father & mother		3.68 (± 0.85)			3.91 (±1.02)			

a ND = non-detectable. Data presented are the mean levels of cholesterol, lipoproteins, and 2-3 DPG, adjusted for age, weight, height, and sex.

b The Total-C/HDL-C for the group with cotinine level <2.5 ng/ml was 3.51, and 3.92 for the group with cotinine level ≥2.5 mg/ml. These values are calculated based on data presented in table (i.e., Table 2 of reference).

* $p<0.05$, ** $p<0.001$

TABLE 8.7
PLATELET SENSITIVITY TO ANTIAGGREGATORY PROSTAGLANDINS[a] BEFORE AND AFTER EXPOSURE TO ETS

Sinzinger (1982) [b]	**Before**	**After**
Exposed to passive smoking		
Nonsmokers	1.26 ± 0.11	2.16 ± 0.21 (p<.01)
Smokers	1.75 ± 0.26	2.08 ± 0.19 (NS)
Burghuber (1986) [c]		
Exposed to active smoking [d]		
Nonsmokers	1.61	2.08 (p<.01)
Smokers	3.33	3.13 (NS)
Exposed to passive smoking [e]		
Nonsmokers	1.25	1.82 (p<.01)
Smokers	1.89	2.04 (NS)

[a] Values represent the concentration of protascyclin necessary to inhibit ADP induced platelet aggregation to 50%. Values are in units of PG in ng/ml platelet rich plasma, means ± serum.

[b] Exposure to passive smoking occurred in a $18m^3$ room were 30 cigarettes were smoked to give a smoke concentration resembling that in discos or restaurants. Subjects were exposed for 15 minutes. Blood was collected before and at the end of the smoking period, as well as 20 and 60 minutes later.

[c] Values shown are calculated in the following way: Sensitivity index of PGI_2 were obtained from extrapolating values in Figures 3 and 4 in reference. From these figures, we estimated that the sensitivity index were 0.62, 0.48, 0.30, 0.32, 0.80, 0.55, 0.53, 0.49 (values are presented in the order under 'Before' and 'After' columns, for each of the 4 rows). Since sensitivity index equals $1/ID_{50}$, where ID_{50} is the concentration of PGI_2 necessary to inhibit ADP-induced platelet aggregation to 50 percent, ID_{50} was calculated is 1/sensitivity index (e.g., 1/0.62=1.61).

[d] Active smoking experiment: Fourteen healthy males smoked two cigarettes within 10 minutes. Blood specimen were collected immediately before and 15 minutes after smoking.

[e] Passive smoking experiment: Twenty-two health males were exposed for 20 minutes in an 18 m^2 room in which 30 cigarettes were smoked. Blood specimen was collected immediately before and 15 minutes after passive smoking period.

TABLE 8.8
MEASURES OF PLATELET FUNCTION IN RELATION TO EXPOSURE TO ACTIVE SMOKING AND PASSIVE SMOKING

			PLATELET FUNCTION	
Study	**Number of Subjects**	**Exposure**	**Endothelial Cells/ Chamber**	**Platelet Aggregate Ratios**
Davis *et al.* (1985)		Smoked tobacco Cigarettes		
	20	Before[a]	2.3 ± 0.5	0.80 ± 0.06
	20	After	4.8 ± 1.3	0.65 ± 0.07
		Smoked non-tobacco cigarettes		
	20	Before	2.5 ± 1.1	0.81 ± 0.10
	20	After	3.0 ± 1.1	0.78 ± 0.10
Davis (1989)		Control Period		
	10	Before	2.2 ± .8	0.88 ± 0.05
	10	After	2.3 ± 1.0	0.88 ± 0.04
		Exposed to ETS[b]		
	10	Before	2.8 ± 0.9	0.87 ± 0.06
	10	After	3.7 ± 1.1	0.78 ± 0.07

[a] All the 'before' and 'after' differences were statistically significant at $p<0.01$.
[b] Nonsmokers were exposed to ETS for 20 minutes in open hospital corridors by sitting next to smokers.

TABLE 8.9
CAROTID ARTERY INTIMAL-MEDIAL THICKNESS (IMT) AS MEASURED BY B-MODE ULTRASOUND IN CURRENT SMOKERS, EX-SMOKERS, NEVER SMOKERS

Study	Number of subjects	Exposure	Mean IMT wall thickness (in mm)	Comments
Howard et al. (1994)	3525 4315 3339 1774	Active smokers Ex-smokers Passive smokers Never smokers not exposed to ETS	0.775 0.772 0.711 0.700	Crude means are shown. The difference between passive smokers and never smokers was 0.011 mm. This difference changed to 0.017mm after adjustment for age, race, and gender ($P \leq 0.0001$) and to 0.014 mm after additional adjustment for lifestyle factors including education, physical activity, alcohol intake, body mass index, and Key's score (P=0.0009).
Diez-Roux et al. (1995)	Males and females 456 448 259 282 77 211	Current smokers in 1987- 1989 Former smokers in 1987-1989 and in 1975 ETS in 1975, 1987-89 ETS in 1987-89 only ETS in 1975 only no ETS	Adjusted means ± standard error 0.807 ± 0.009 0.757 ± 0.009 0.734 ± 0.012 0.738 ± 0.011 0.731 ± 0.022 0.706 ± 0.013	Mean wall thickness was adjusted for gender, age, systolic blood pressure, LDL cholesterol, presence of Key's score, physical activity scores, alcohol intake and education using multiple linear regression.

TABLE 8.10
ENDOTHELIUM-DEPENDENT ARTERIAL DILATATION
IN ACTIVE SMOKERS, NEVER SMOKERS EXPOSED TO ETS, AND NEVER SMOKERS NOT EXPOSED

Study	Number of Subjects	Exposure	Flow-mediated dilatation (mean values ± SD; in %)
Celermajer et al. (1996)	26	• Active smokers	4.4* ± 3.1
	26	• Never smokers exposed to ETS	3.1* ± 2.7
	26	• Never smokers not exposed to ETS	8.2 ± 3.1
		By gender	
	13	• Never smokers exposed to ETS	3.2 ± 2.5
	13	Males	3.0 ± 2.9
		Females	
	13	• Never smokers not exposed to ETS	7.3 ± 1.9
	13	Males	9.1 ± 3.9
		Females	
	9	By level of ETS exposure	4.1 ± 3.3
	9	• Never smokers exposed to ETS	3.1 ± 2.2
	8	Light[a]	1.8 ± 2.0
		Moderate[b]	
		Heavy[c]	

a "Light" is defined as never smokers who were exposed to 1 to 3 hours of ETS at home or at work for at least 3 years
b "Moderate" is defined as never smokers who were exposed to 4 to 6 hours of ETS at home or at work for at least 3 years
c "Heavy" is defined as never smokers who were exposed to > 6 hours of ETS at home or at work for at least 3 years
* P value < 0. 05 for never smokers exposed to ETS compared to never smokers not exposed, and for active smokers compared to never smokers not exposed to ETS.

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